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STUDY OF MICROENCAPSULATED PRODUCTS WITH RESPECT TO THEIR ABILITY TO PREVENT INCOMPATIBILITIES

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STUDY OF MICROENCAPSULATED PRODUCTS WITH RESPECT TO THEIR ABILITY TO PREVENT INCOMPATIBILITIES

BY

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ABSTRACT

The interaction between drugs and excipients or between drugs and other drugs in the same dosage form have potential to modify safety and efficacy. In some cases the interaction can be of such a degree as to preclude the use of some excipients or to dramatically reduce the shelf life of the products. Thus there is clearly a need for techniques which can reduce or eliminate such interactions.

Sometimes the irrational combination of two drugs or drug and excipient cause a decrease in the stability, bioavailability and efficacy of the dosage form [1]. Microencapsulation can be considered as a tool to enhance the drug stability [2]. It has generally been observed that microencapsulated products show a substantial reduction or elimination of the adverse effects of incompatibilities, although quantitative data on the extent of stabilization is not readily available in the published literarture.

The primary objective of this study was to determine the drug interactions and incompatibilities between drugs and excipients which are widely used in pharmaceutical manufacturing and have some characteristic compatibility problems. I did these studies on powder mixes and compressed tablets owing to the fact that majority of the dosage forms are formulated in the solid state [3]. The study included three drugs namely aspirin, acetaminophen and pseudoephedrine (hydrochloride salt).

The interaction between aspirin and dibasic calcium phosphate (Emcompress) was studied in detail. Non - microencapsulated aspirin showed significant degradation by hydrolysis in presence of Emcompress at room temperature as well as elevated temperature. Microencapsulated aspirin

showed a marked decrease in the degradation under same conditions.The stabilizing effect of the microencapsulation was both statistically significant and substantial.

The interaction between acetaminophen (APAP) and diphenhydramine hydrochloride and phenylephrine hydrochloride was monitored for the presence of degradation products. These agents showed incompatibility with acetaminophen when used in the proportion which was the same as that of an over the counter product. The manifestation of incompatibility was melting point depression by eutectic formation. The eutectic formation was prevented when microencapsulated acetaminophen was used.

Non - microencapsulated acetaminophen showed significant adsorption over antacids like aluminum hydroxide, magnesium trisilicate and calcium carbonate. Microencapsulated acetaminophen demonstrated appreciable decrease in the rate and extent of adsorption under similar conditions.

I had planned the compatibility studies of pseudoephedrine HCl with hydrous lactose and with sodium metabisulphite. The literature showed evidence of some degradation products. However initial tests showed no significant compatibility problems and hence no further experimentation was performed on these substances. However the interaction of pseudoephedrine and acetaminophen and pseudoephedrine and aspirin was monitored for the degradation products.

A battery of in process quality control tests such as appearance, weight variation, content uniformity, surface characters, flowability, friability, and moisture content were performed on all three formulations. All results were evaluated using conventional statistical techniques using factorial design and

the differences between microencapsulated and non microencapsulated products were determined at 95 % confidence intervals. Both the groups were compared using tests such as ANOVA (Analysis of Variance), Student's t test (two tailed), and simple regraession analysis with the help of a software on a microcomputer.

ACKNOWLEDGMENTS

I want to express my profound appreciation for not only the guidance of my major professor, Dr. Christopher T. Rhodes but also his support of all my endeavors. Without the help of Dr. Rhodes, my progress over the last two and a half years would have been stunted. I found an excellent teacher and great advisor in him. I would like to thank Dr. Sam Ghanta, R & D director of Eurand America for his guidance and financial support without which this work would not have been completed. I also would like to thank Dr. Norman Campbell and Dr. Sara Rosenbaum for serving on my M. S. thesis Committee.

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All my colleagues and friends in the department of pharmaceutics and the URI community deserve a special note of thanks. I would like to thank Dnyanesh, Dr. Kottke, Carl, George, Polireddy, Suresh, Alpana, Lin, & Dr. Anita Nanda for their continued support and encouragement throughout my graduate studies.

My family members and friends back home in India were the constant source of understanding, love and support in my career. They significantly helped mold my career and outlook towards life. I greatly appreciate their utmost patience and trust in me.

Finally I would like to dedicate this work to my dearest mother who means everything in life to me. Whatever little success I have achieved in my life and career is because of her. I really feel proud to be the son of such a wonderful and loving mother.

PREFACE

This thesis is prepared according to the manuscript format which is permitted under section 11 - 3 of the Graduate Manual of the University of Rhode Island. The Manuscript will be submitted for publication in Drug Development & Industrial Pharmacy.

Some of the experimental data in this thesis was presented as a poster in eighth annual meeting and exposition of the American Association of Pharmaceutical Scientists. (AAPS) held at Orlando, Florida in November 1993.

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STUDY OF MICROENCAPSULATED PRODUCTS WITH RESPECT TO THEIR ABILITY TO PREVENT INCOMPATIBILITIES

ABSTRACT

The primary objective of this study was to determine the drug interactions and incompatibilities between the drugs and drugs and excipients which have some characteristic compatibility problems. This study included three of such drugs namely aspirin, acetaminophen (APAP) and pseudoephedrine hydrochloride. It consisted of series of comparative laboratory experiments for the manifestation of incompatibilities or lack thereof in (1) powder mixes and (2) compressed tablets. The selected drugs were used as powders and in the form of microencapsules. The study was conducted at room temperature as well as at 40 C and 60 % R. H. (relative humidity)

The important degradation pathway for aspirin is hydrolysis. The hydrolysis of aspirin in presence of dibasic calcium phosphate was studied. Aspirin hydrolized producing 39 % degradation at room temperature and 53% at elevated temperature. In case of microencapsulated aspirin sample, it was 26 % at room temperature and 28 % at elevated temperature. All samples were analyzed initially and after three months. The avarage salicylic acid build up in both cases was under the pharmacopoeal limits.

The interaction of acetaminophen with various antacids was monitored. The manifestation of interaction was the adsorption of the drug on the antacid. The antacids tested were calcium carbonate (1) , aluminum hydroxide (2) and magnesium trisilicate (3). In case of non - microencapsulated acetaminophen sample the adsorption of the drugs was found to be 7 % on (1), 18 % on (2) and 15 % on (3). In case of microencapsulated acetaminophen sample the adsorption was 2 % on (1), 1.5 % on (2) and 1.6 % on (3). The interaction between acetaminophen with diphenhydramine

hydrochloride and phenylephrine hydrochloride was characterized by melting point depression due to eutectic formation. The eutectic formation was not observed in microencapsulated acetaminophen samples. From these studies conclusion was made that microencapsulated samples showed substantial reduction and in some cases, elimination of the adverse effects of incompatibilities.

INTRODUCTION

Microencapsulation may be thought of as a method of wrapping small entities in individual protective coatings [4]. In microencapsulation a relatively thin coating is applied to small particles of solids or droplets of liquids and dispersions. It is arbitrarily differentiated from macroencapsulation in that the former involves the coating of the particles ranging dimmensionally from several tenths of a micrometer to about 5000 μ.[5,6].

In pharmaceutical preparations the uniqueness of microencapsules lies in the size of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms [8]. Due to the use of these discrete particles, drug moieties can be widely distribiuted throughout the gastrointestinal tract. This potentially improves drug absorption and reduces side effects related to localized build up of irritating drugs against the gastrointestinal mucosa.

In the U. S. A. the majority of the drugs which are in over the couter (OTC) market are combination products [9]. Sometimes the irrational combination of two drugs or drug - excipient leads to a decrease in the stability, bioavailability and efficacy of the dosage form [10]. It has generally been observed that microencapsulated products show a substantial reduction or elimination of the adverse effects of incompatibilities, however the published literature does not appear to have quantitative data substantiating this point.

The compatibility studies mentioned above involved powder mixes and tablet dosage forms owing to the fact that majority of the dosage forms are formulated in the solid state [11]. Any reaction occuring in the solid state will assume dramatically different characteristics from the same reaction

proceeding under a liquid or gaseous state [12]. Solid state reaction have long maintained a poorly defined terrain on chemical landscape. However difficult to define quantitatively, interactions between solids present a new frontier in the investigation in the chemical behaviour. The primary objective of this study was to determine the drug interactions and incompatibilities between drugs and excipients which are widely used in the pharmaceutical manufacturing and have some characteristic compatibility problems. This study included three of such commercially important drugs. They are aspirin, acetaminophen and pseudoephedrine hydrochloride.

A literatute search has shown that these drugs have some characteristic compatibility problems with commonly used excipients such as dibasic calcium phosphate (Emcompress)[13] , hydrous lactose [14] ,sodium metabisulphite and magnesium stearate[15] . There is also a sufficient evidence that these drugs interact with other classes of drugs such as antacids, antihistamines and decongestants. This study involved calcium carbonate, aluminum hydroxide and magnesium trisilicate as antacids, diphenhydramine hydrochloride as antihistaminic and phenylephrine hydrochloride as decongestatnt. Solid dosage forms containing aspirin, acetaminophen and pseudoephedrine comprise a significant portion of todays OTC market. Thus it becomes very important to investigate the field of drug interactions occuring in these drugs if they are to be formulated in the solid dosage forms.

MATERIALS AND METHODS

This study involved a series of comparative laboratory experiments for the manifestation of incompatibilities or lack thereof in

a) Powder mixes

b) Direct compression tablets.

The selected drugs were used as powders and in the form of microencapsules. The laboratory investigation was made in four types of systems for each drug.

a) Powder mixes using non - microencapsulated drug.

b) Powder mixes using microencapsulated drug.

c) Compressed tablets made using non - microencapsulated drug.

d) Compressed tablets made using microencapsulated drug.

The non - microencapsulated and microencapsulated drugs were obtained from Eurand America, Vandalia, Ohio. All other materials were purchased from commercial sources, mainly from Fisher Scientific, Springfield, New Jersey. All other solvents and reagents used were of HPLC grade.

The powders and tablets of the three drugs were evaluated at the time of preparation in terms of potency, flowability, appearance, hardness, friability, weight variation and content uniformity. They were also evaluated at intervals during storage at ambient temperature and also at 40 ^{0} C / 60 % relative

humidity for a period of eight weeks in order to determine the ralative rate of change between both the types of systems.

The following methods were used for the camparision of microencapsulated and non - microencapsulated formulations.

1) Macroscopic evaluation :

Samples were subjected to visual observation in triplicate. The macroscopic observation was done for the determination of possible changes in crystalinity, liquifaction, hygroscopicity etc.

2) Dissolution tests :

Dissolution tests were carried out by using Vanderkamp dissolution test apparatus with standard USP basket assembly. The dissolution medium was distilled water and the studies were done at 37 ^{0} C. at 100 RPM.

3) Ultra Violet Spectroscopy (UV) :

Ultra violat spectroscopy was used to monitor the interaction between aspirin and dibasic calcium phosphate (Emcompress). It was also used for the quantification of the interaction between acetaminophen and various antacids. The antacids used were aluminum hydroxide, calcium carbonate and magnesium trisilicate.

For the intercation between aspirin and dibasic calcium phosphate, the samples were prepared by mixing equal portions of aspirin and Emcompress. They were then mixed in a turbula mixer for about one hour. Portions of 200 mg. were taken in 5 ml. open vials. The vials were placed in constant temperature and relative humidity (45 ^{0} C. and 55 % R. H.). They were then

removed initially and then at at regular time intervals and analyzed spectrophotometrically in 95 % ethanol at 302 nm.

The validation of the assay was done in order to determine the content of salicylic acid which is a degradation product of aspirin hydrolysis.The method employed was as follows. UV absorbance spectra of aspirin and salicylic acid were obtained for determination of their respective lambda max. They were 258 and 302 nm. respectively. Samples were removed initially and then at regular time intervals. They were diluted appropriately with ethanol and analyzed spectrophotometrically by Hawlett Peckard 8451 A diode array spectrophotometer. The amount of salicylic acid formed was determined by the method of simultaneous equations using molar absorptivities.

Elaborate study was performed on the interaction of acetaminophen with different antacids. The UV determination was done as follows. A standard calibration curve was plotted for both, the microencapsulated and non - microencapsulated acetaminophen each time befor the intercation with each antacid. Specific amount of drug solution was mixed with antacid and was rotated in a rotating assembly at 37 ^{0}C. at 60 RPM. The contents were filtered by nylon 6 filter membrane with a pore soze of 0.45 μ.and analyzed spectrophotometrically at 244 nm. Blank correction was done each time and for each antacid to eliminate the influence of water soluble impurities present in the antacid. Attempt was made to determine if there is prevention or decrease in adsorption due to microencapsulation.

4) Differential Scanning Calorimetry (DSC) :

Differential scanning calorimetry was used for the determination of the interaction between acetaminophen and diphenhydramine hydrochloride and acetaminophen and phenylephrine hydrochloride. Work was done upon both, microencapsulated and non-microencapsulated acetaminophen. The instrumentation was Perkin Elmer DSC - 2 with Linear 1200 chart recorder. The heating rate was 5 ^{0} C / min. and the temperature range was 30 ^{0} C. to 250 ^{0} C. The chart speed was 2 cm / sec. and the sensetivity of the instrument was 10 m. cal. / deg. The experiment was carried our in an inert atmosphere with the supply of nitrogen gas. About 25 mg. of sample was subjected to DSC each time. The content uniformity of the samples were determined by the endothermic peaks obtained. The results were obtained in duplicates. The manifestation of interaction between acetaminophen and above mentioned drugs was melting point depression due to the formation of eutectic mixture. Attempt was made to determine if there is prevention or decrease in the severity of the interaction due to microencapsulation.

5) Scanning Electron Microscopy (SEM) :

The microencapsules of aspirin, acetaminophen and pseudoephedrine were mounted on a carbon tape and sputter coated with Gold : Palladium (60 : 40) in an Edward's S150 B sputtum coater. The analysis was done by examining the samples in the scanning mode with a JEOL 1200 EX scanning / transmission electron microscope operating at 60 KV.

6) Statistical Evaluation :

Statistical evaluation of the interaction between aspirin and dibasic calcium phosphate was done using Student's t test with a α value of 0.01. The evaluation of the interaction between the acetaminophen and various antacids was done by using Analysis Of Variance (ANOVA).

RESULTS

Figure 1 to 3 shows the scanning electron micrographs (SEM) of the microencapsules of aspirin, acetaminophen and pseudoephedrine hydrochloride respectively.

Fig. 1 gives the micrograph of aspirin, characterized by regular needle shaped crystals ranging from 500 to 2000 microns in length and 25 to 200 microns in width. The coat over these crystals is evident as seen in the photograph. We also found some small irregular crystals clustered in a group between the large needle shaped crystals. Some surface irregularities are also seen in the micrograph.

Fig. 2 gives SEM of microencapsulated acetaminophen. The sample is charecterized by small irregular crystals clustered in a group. The average size ranges from 100 to 500 microns in length and about 50 to 300 microns in width. The coating over the crystals appear to be thick and smooth.

Figure 3 represents SEM of pseudoephedrine hydrochloride. The sample consists of needle shaped round and irregular crystals ranging from 100 to 750 microns in length. The coating of the encapsulating material is seen clearly from the photograph.SEM profile analysis was done at 50, 200 and 3000 times magnification.

Figure 4 shows differential scanning thermogram of non - microencapsulated acetaminophen (1), diphenhydramine hydrochloride (2) and 1 : 1 physical mixtre. Non - microencapsulated acetaminophen showed a characteristic

endothermic peak at 172 ^{0} C. Diphenhydramine hydrochloride showed a peak at 167 ^{0} C. When 1 : 1 physical mixture was subjected to DSC, the endothermic peak is observed at 98 ^{0} C. Figure 5 shows differential scanning thermogram for the microencapsulated acetaminophen (1), diphenhydramine hydrochloride (2) and 1 : 1 physical mixture (3). The microencapsulated acetaminophen showed an endothermic peak at 173 ^{0} C. The 1 : 1 physical mixture showed broad endothermic peak between 143 to 146 ^{0} C.Figure 6 shows DSC thermogram for the acetaminophen - phenylephrine hydrochloride combination. It shows an endothermic peak at 172 ^{0} C for non microencapsulated acetaminophen (1), 147 ^{0} C for phenylephrine hydrochloride (2) and 122 ^{0} C for1 : 1 physical mixture (3)

Figure 7 represents the DSC thermogram when acetaminophen is microencapsulated. The micrpencapsulated acetaminophen showed a peak at 172 ^{0} C. 1 : 1 physical mixture showed endothermic peak at 152 ^{0} C.

Table 1 shows percentage degradation of aspirin in presence of dibasic calcium phosphate in powder mixes. The concentration range was 5 µg / ml. to 25 µg / ml The mean percentage degradation was found to be 42 % at room temperature and 54 % at elevated temperature for non - microencapsulated aspirin. For aspirin microencapsules the values were 27 % and 33 % respectively. The two treatments were compared using Student's t test.(Table 4).The p value for this statistic was found to be 0.004 indicating that the probability that there is no difference between the two data sets is 0.004.

Table 2 shows percentage degradation of aspirin in presence of Emcompress in direct compression tablets. Same concentration range as in case of powder

mixes was selected. The mean percentage degradation in this case was found to be 39 % at room temperature and 53 % at elevated temperature when non- microencapsulated aspirin was used. In case of microencapsulated aspirin the values were 26 % and 28 % respectively. When the two treatments were compared with Student's t test (Table 4). The p value was found to be 0.006 %.

Figure 8 shows the dissolution profile of non-microencapsulated and microencapsulated acetaminophen tablets at room temperature in presence of aluminum hydroxide. Figure 9 shows the dissolution profile of non microencapsulated and microencapsulated acetaminophen tablets at elevayed temperature in presence of aluminum hydroxide. For non - microencapsulated acetaminophen, the percentage dissolution after 45 mins.was 78 % for the samples kept at room temperature and 82 % for samples kept at elevated temperature. For microencapsulated acetaminoiphen the values were found to be 94 % and 95 % respectively. As seen from figures 8 and 9, all the profiles were compared with acetaminophen control.

Figure 10 shows dissolution profile of non-microencapsulated and microencapsulated acetaminophen tablets at room temperature in presence of calcium carbonate. Non - microencapsulated acetaminophen showed 89 % dissolution for samples kept at room temperature and 90 % dissolution for samples stored at elevated temperature. Figure 11 shows dissolution profile of non - microencapsulated and microencapsulated acetaminophen tablets at elevated temperature in presence of calcium carbonate. For microencapsulated acetaminophen the percentage dissolution was 94 % for samples stored at room temperature and 97 % for the samples stored at

elevated temperature. Both the dissolution profiles were compared with acetaminophen control.

Figure 12 shows dissolution profile of non - microencapsulated and microencapsulated acetaminophen tablets at room temperature in presence of magnesium trisilicate. The percentage dissolution was 82 % for the samples kept at room temperature and 83 % for the samples kept at elevated temperature. Figure 13 shows dissolution profile of non - microencapsulated and microencapsulated acetaminophen tablets at elevated temperature in presence of magnesium trisilicate. Microencapsulated acetaminophen showed 94 % dissolution for the samples kept at room temperature and 94 % dissolution for the samples kept at elevated temperature. Both the dissolution profiles were compared with acetaminophen control.

Table 3 shows the interaction of acetaminophen with different antacids in the powder mixes. In case of non microencapsulated acetaminophen and aluminum hydroxide powder mix the percentage of drug adsorbed over the antacid was found 14 %. Use of microencapsulated acetaminophen decreased this adsorption to 4 %. Similarly for non - microencapsulated and microencapsulated acetaminophen with aluminum hydroxide mix the values were 5 % and 2 % respectively. When the antacid was magnesium trisilicate, the values were 24 % and 8 % respectively.The statistical evaluation of these interactions was done by using ANOVA. (Analysis of Variance) Tables 5 , 6 and 7 shows the results obtained form ANOVA.

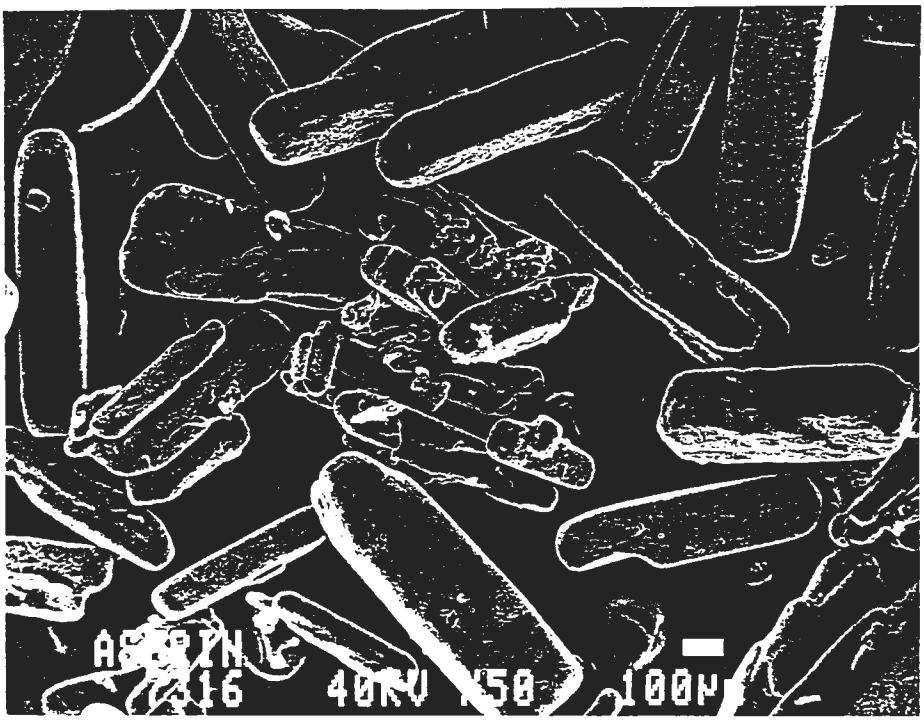


FIGURE 1 Scanning electron micrograph of the crystals of microencapsulated aspirin (magnified 50 times) taken with a JEOL 1200 EX electron microscope.

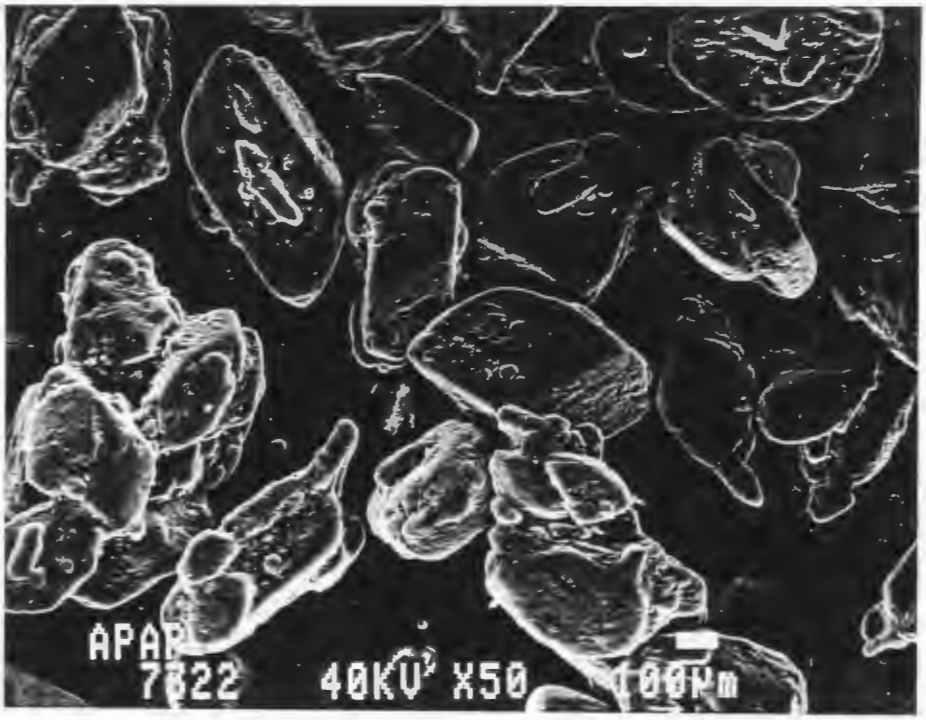


FIGURE 2 Scanning electron micrograph of the crystals of microencapsulated acetaminophen (magnified 50 times) taken with a JEOL 1200 EX electron microscope.

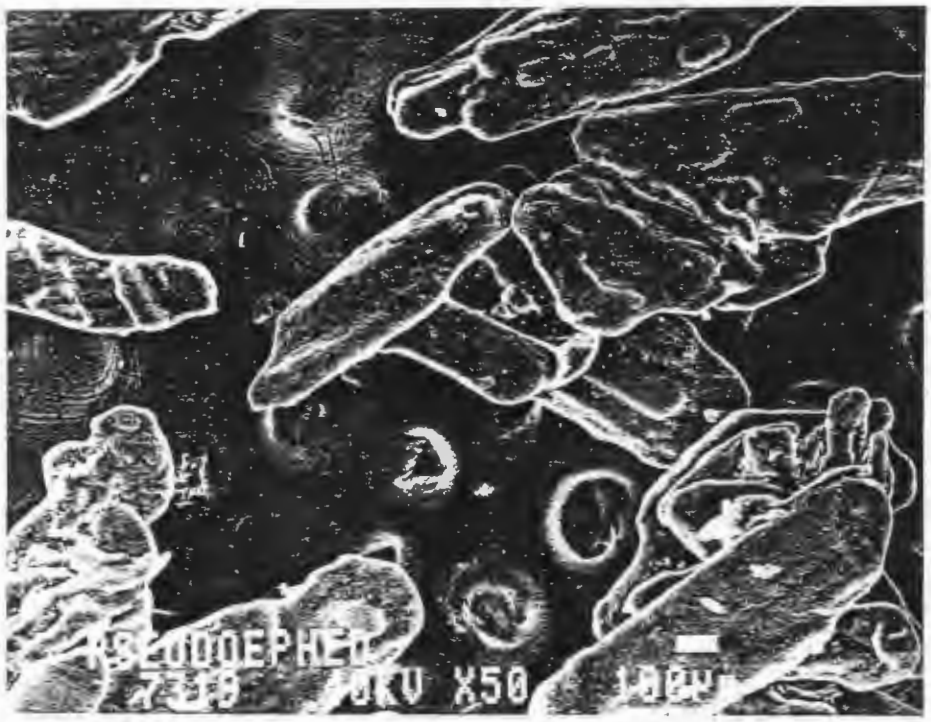


FIGURE 3 Scanning electron micrograph of the crystals of microencapsulated pseudoephedrine hydrochloride (magnified 50 times) taken with a JEOL 1200 EX electron microscope.

TABLE 1 Percentage degradation of aspirin in presence of dibasic calcium phosphate (Emcompress) in powder mixture :

Concentration	Non micro - encapsulated aspirin	Non micro - encapsulated aspirin	Aspirin micro-encapsules	Aspirin micro-encapsules
	Samples at room temp.	samples at elevated temp.	sample at room temp.	samples at elevated temp.
5 µg. / ml.	43 %	55 %	37 %	40 %
10 µg. / ml.	48 %	59 %	25 %	33 %
15 µg. / ml.	36 %	47 %	21 %	28 %
20 µg. / ml.	44 %	51 %	24 %	30 %
25 µg. / ml.	39 %	49 %	27 %	25 %
Mean	42 4 %	54.8 %	27.1 %	33.5 %
S. D.	9.2	11.2	6.2	6.2

TABLE 2 : Percentage degradation of aspirin in presence of dibasic calcium phosphate (Emcompress) in direct compression tablets:

Concentration	Non micro - encapsulated aspirin	Non micro - encapsulated aspirin	Aspirin micro - encapsules	Aspirin micro - encapsules
	Samples at room temp.	Samples at elevated temp.	Samples at room temp.	Samples at elevated temp.
5 µg. / ml.	42 %	55 %	31 %	40 %
10 µg. / ml.	41 %	57 %	35 %	33 %
15 µg. / ml.	34 %	55 %	20 %	29 %
20 µg. / ml.	38 %	49 %	20 %	27 %
25 µg. / ml.	40 %	51 %	25 %	24 %
Mean	39.1 %	53.4 %	26.4 %	28.1 %
S. D.	6.3	8.6	10.3	11.2

TABLE 3 : Interaction of acetaminophen with various antacids in the powder form

Combination	Percentage drug adsorbed on antacid
Unencapsulated acetaminophen and aluminum hydroxide	14 %
Encapsulated acetaminophen and aluminum hydroxide	4 %
Unencapsulated acetaminophen and calcium carbonate	5 %
Encapsulated acetaminophen and calcium carbonate	2 %
Unencapsulated acetaminophen and magnesium trisilicate	24 %
Encapsulated acetaminophen and magnesium trisilicate	8 %

TABLE 4 : Student's t test for microencapsulated and non - microencapsulated aspirin in presence of Emcompress

a) Powder mixes

Non - microencapsulated Vs microencapsulated at room temperature

Deg. of Freedom	Mean X - Y	Paired t value	Prob. (2 - tail)
4	15.2	5.084	0.0071

Non - microencapsulated Vs microencapsulated at elevated temperature.

Deg. of Freedom	Mean X - Y	Paired t value	Prob. (2 - tail)
4	21	10.917	0.0004

b) Direct compression tablets

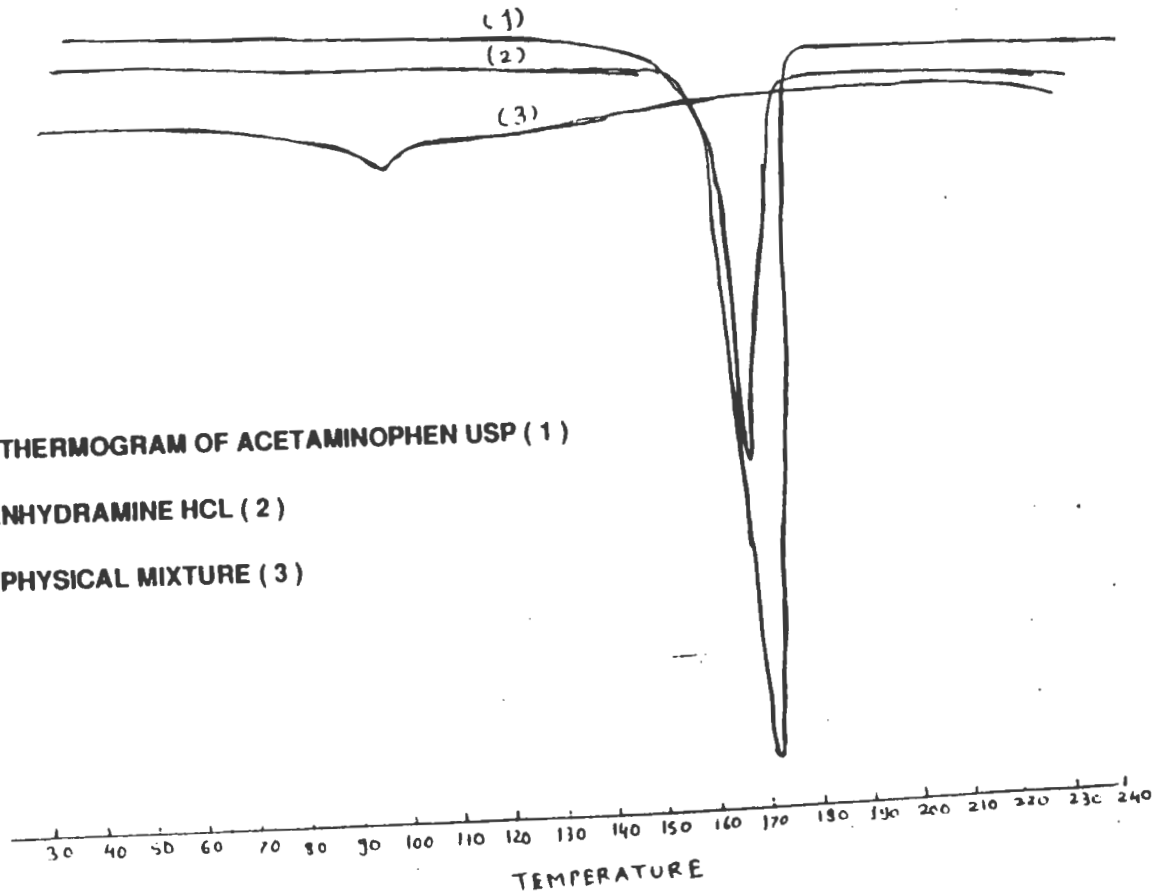
Non - microencapsulated Vs microencapsulated at room temperature

Deg. of Freedom	Mean X - Y	Paired t value	Prob (2 - tail)
4	12.8	6.291	0.0033

Non - microencapsulated Vs microencapsulated at elevated temperature

Deg. of Freedom	Mean X - Y	Paired t value	Prob (2 - tail)
4	22.8	10.701	0.004

FIGURE 4 Differential scanning calorimeter thermogram of non microencapsulated acetaminophen (labelled as 1) , Diphenhydramine hydrochloride (Labelled as 2) and 1 : 1 physical mixture of the two drugs. (labelled as 3). The scale at the bottom shows temperature in degree centigrades.

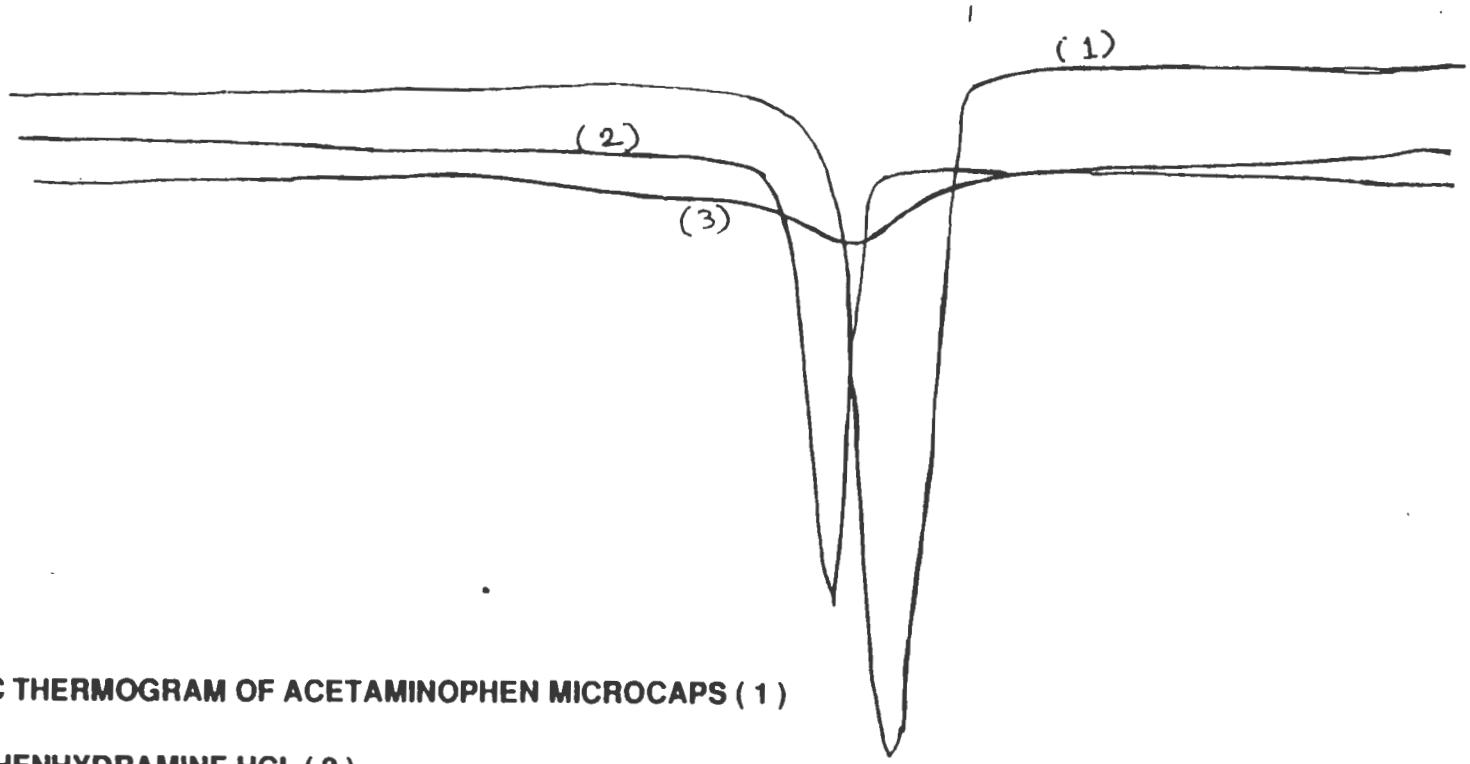


DSC THERMOGRAM OF ACETAMINOPHEN USP (1)

DIHENHYDRAMINE HCL (2)

1 : 1 PHYSICAL MIXTURE (3)

FIGURE 5 Differential scanning calorimeter thermogram of microencapsulated acetaminophen (labelled as 1) , Diphenhydramine hydrochloride (Lebelled as 2) and 1 : 1 physical mixture of the two drugs. (labelled as 3). The scale at the bottom shows temperature in degree centigrades.

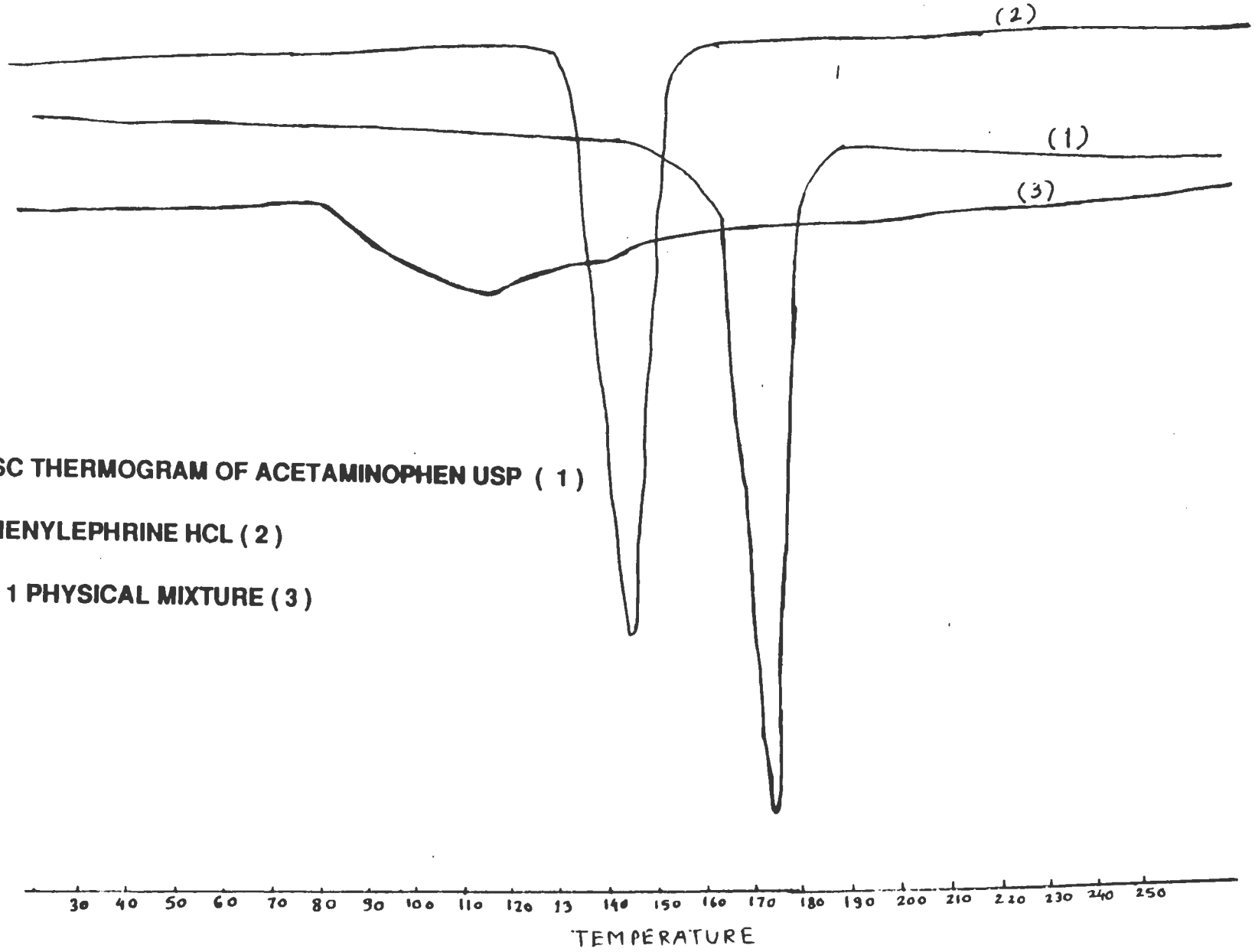


DSC THERMOGRAM OF ACETAMINOPHEN MICROCAPS (1)

DIPHENHYDRAMINE HCL (2)

1 : 1 PHYSICAL MIXTURE

FIGURE 6 Differential scanning calorimeter thermogram of non microencapsulated acetaminoiphen (labelled as 1) , Phenylephrine hydro - chloride (labelled as 2) and 1 : 1 physical mixture (labelled as 3). The scale at the bottom shows the temperature in degrees centigrade.

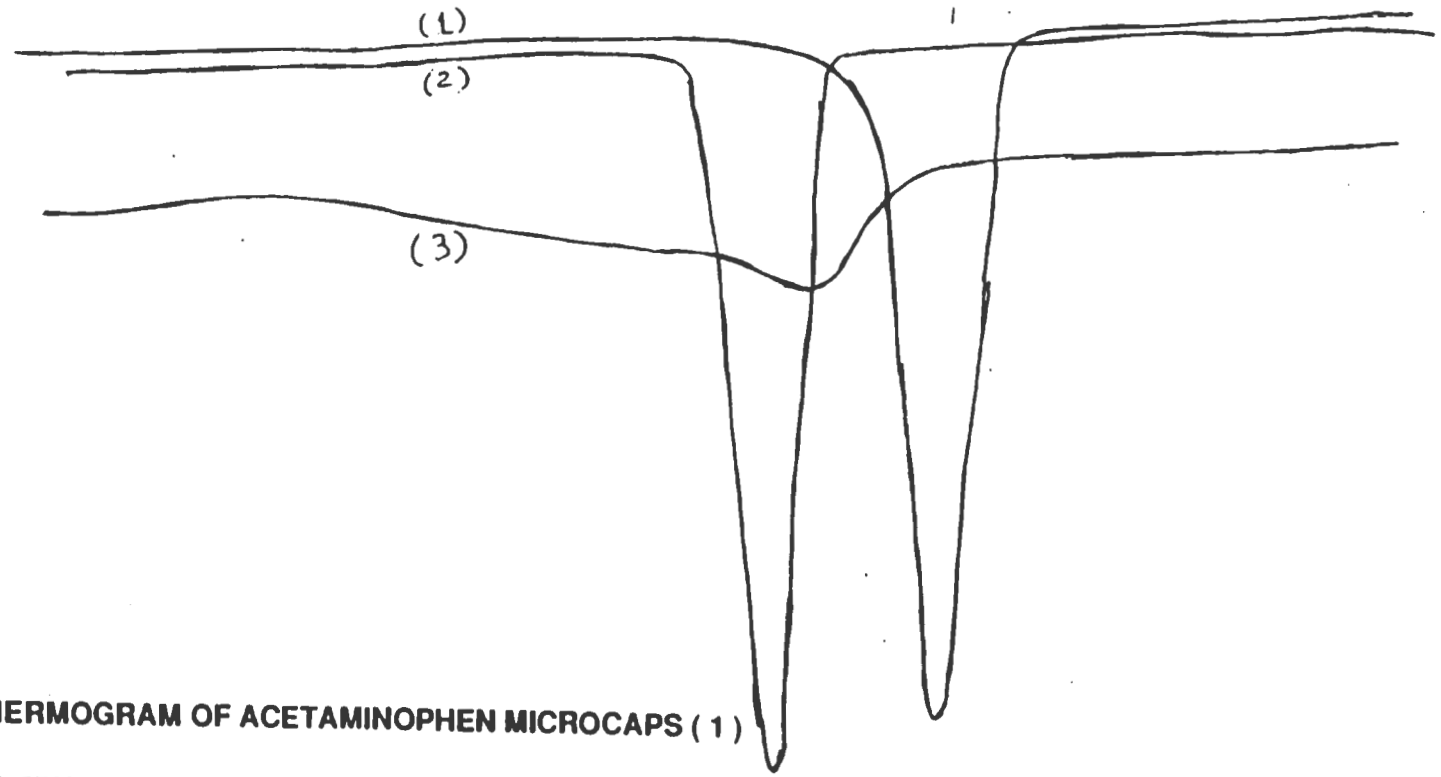


DSC THERMOGRAM OF ACETAMINOPHEN USP (1)

PHENYLEPHRINE HCL (2)

1 : 1 PHYSICAL MIXTURE (3)

FIGURE 7 Differential scanning calorimeter thermogram of non microencapsulated acetaminoiphen (labelled as 1) , Phenylephrine hydro - chloride (labelled as 2) and 1 : 1 physical mixture (labelled as 3). The scale at the bottom shows the temperature in degrees centigrade.



DSC THERMOGRAM OF ACETAMINOPHEN MICROCAPS (1)

PHENYLEPHRINE HCL (2)

1 : 1 PHYSICAL MIXTURE (3)

TABLE 5: ANOVA of microencapsulated and non - microencapsulated acetaminophen in presence of aluminum hydroxide

Source of variation	Degree of Freedom	Sum of squares	Mean square	F value	P value
Temperature	1	5.311	5.311	142.5	0.00
Formulation	1	0.113	0.113	3.045	0.0963
TF	1	0.711	0.711	19.075	0.0003

TABLE 6: ANOVA of microencapsulated and non - microencapsulated acetaminophen in presence of calcium carbonate

Source of variation	Degree of Freedom	Sum of squares	Mean square	F value	P value
Temperature	1	0.211	0.211	9.209	0.0065
Formulation	1	0.155	0.155	6.776	0.0065
TF	1	3.912	3.912	170.8	0.00

TABLE 7 : ANOVA of microencapsulated and non - microencapsulated acetaminophen in presence of magnesium trisilicate

Source of variation	Degree of Freedom	Sum of squares	Mean square	F value	P value
Temperature	1	8.821	8.812	419.0	0.00
Formulation	1	0.886	0.886	42.11	0.00
TF	1	0.760	0.760	36.13	0.00

FIGURE 8 Comparision of the dissolution profiles of non microencapsulated and microencapsulated acetaminophen tablets at room temperature in presence of aluminum hydroxide. The abscissa indicates time in minutes and the ordinate shows cumulative percent release of the drug. The acetaminophen control is labelled as APAP CONTROL where as the dissolution profiles of non microencapsulated and microencapsulated acetaminophen are labelled as N. M. AT R. T. and M. AT R. T respectively.

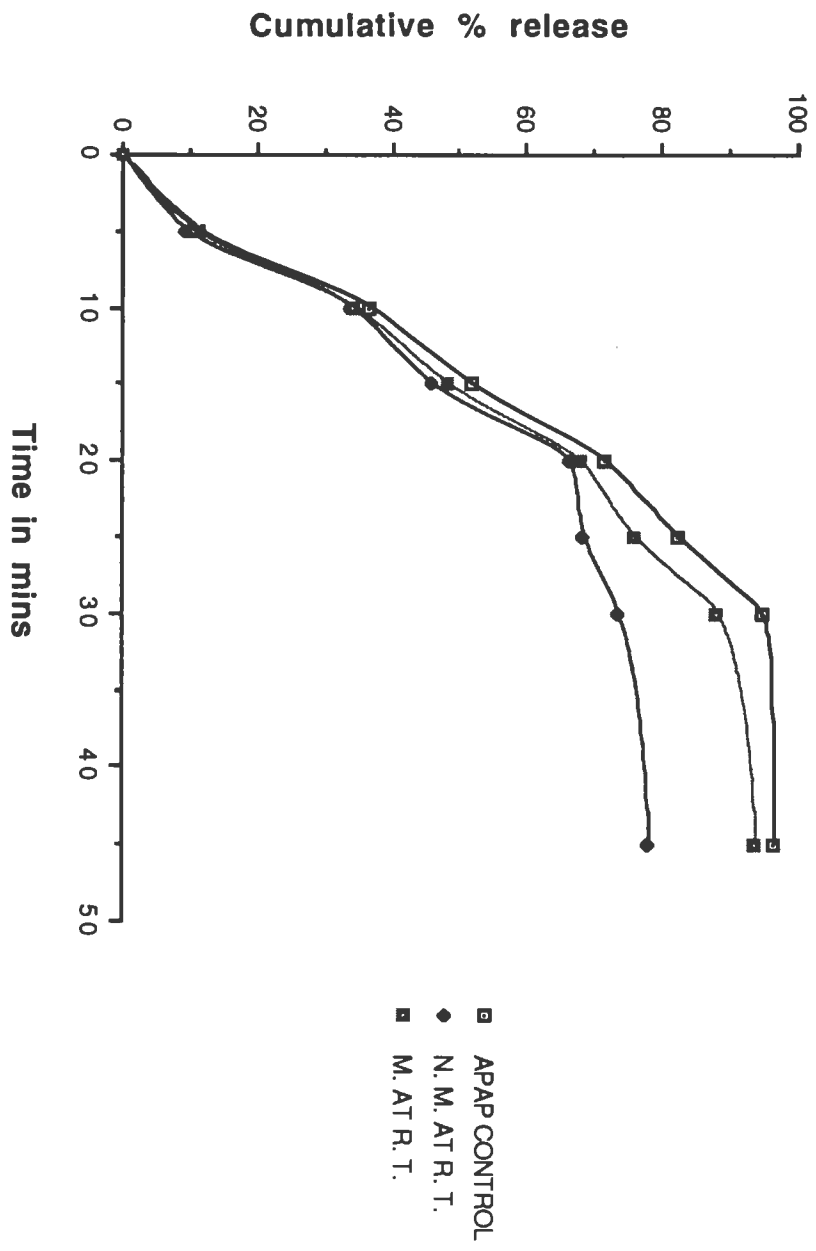

Cumulative % release
0
20
40
60
80
100
0
10
20
30
40
50
Time in mins
APAP CONTROL
N. M. AT R. T.
M. AT R. T.

FIGURE 9 Comparision of the dissolution profiles of non microencapsulated and microencapsulated acetaminophen tablets at elevated temperature in presence of aluminum hydroxide. The abscissa indicates time in minutes and the ordinate shows cumulative percent release of the drug.The acetaminophen control is labelled as APAP CONTROL where as the dissolution profiles of non microencapsulated and microencapsulated acetaminophen are labelled as N. M. AT E. T. and M. AT E. T. respectively.

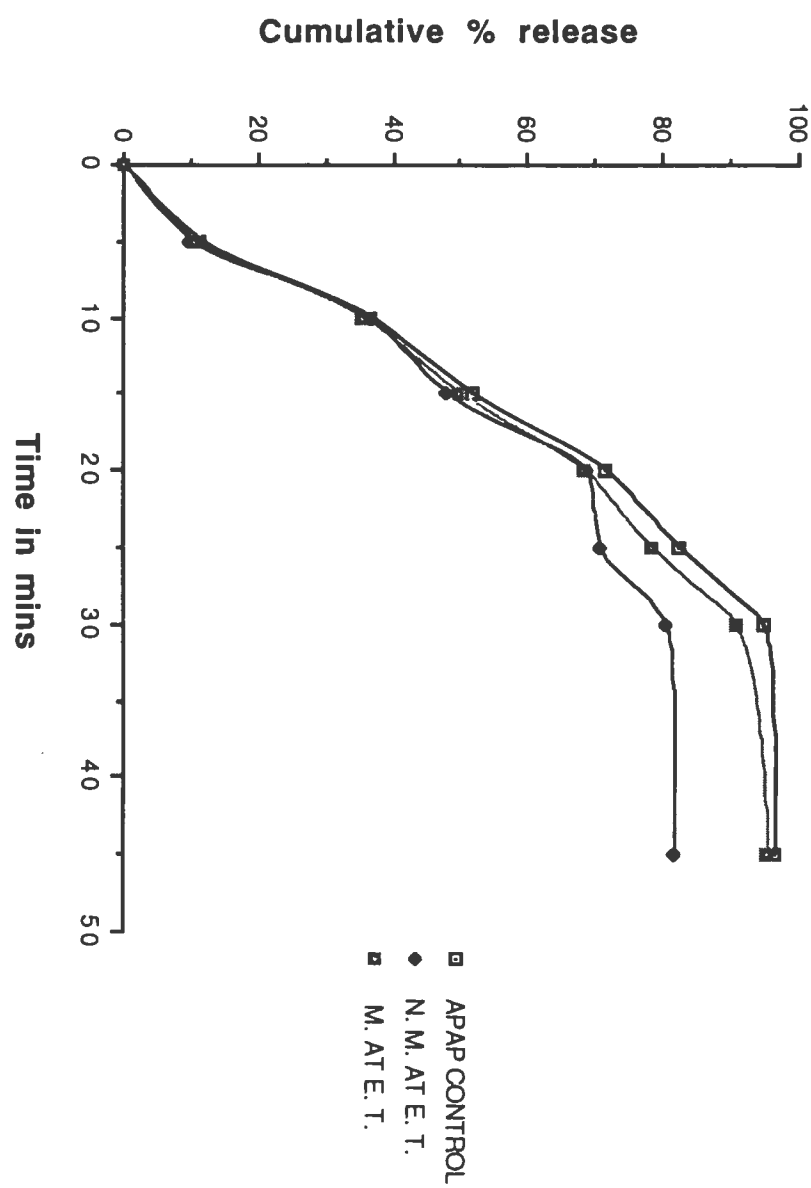

Cumulative % release
0
20
40
60
80
100
0
10
20
30
40
50
Time in mins
APAP CONTROL
N. M. AT E. T.
M. AT E. T.

FIGURE 10 Comparision of the dissolution profiles of non microencapsulated and microencapsulated acetaminophen tablets at room temperature in presence of calcium carbonate.The abscissa indicates time in minutes and the ordinate shows cumulative percent release of the drug.The acetaminophen control is labelled as APAP CONTROL where as the dissolution profiles of non microencapsulated and microencapsulated acetaminophen are labelled as N. M. AT R. T. and M. AT R. T. respectively.

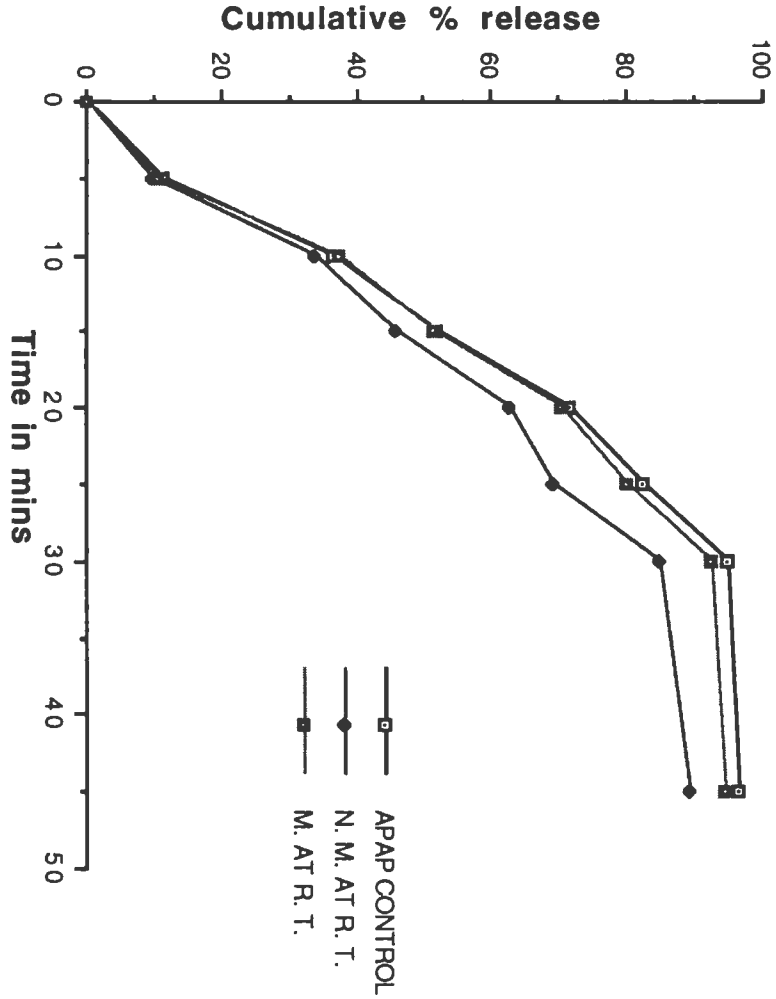

Cumulative % release
0
20
40
60
80
100
Time in mins
0
10
20
30
40
50
APAP CONTROL
N. M. AT R. T.
M. AT R. T.

FIGURE 11 Comparision of the dissolution profiles of non microencapsulated and microencapsulated acetaminophen tablets at elevated temperature in presence of calcium carbonate The abscissa indicates time in minutes and the ordinate shows cumulative percent release of the drug.The acetaminophen control is labelled as APAP CONTROL where as the dissolution profiles of non microencapsulated and microencapsulated acetaminophen are labelled as N. M. AT E. T. and M. AT E. T. respectively.

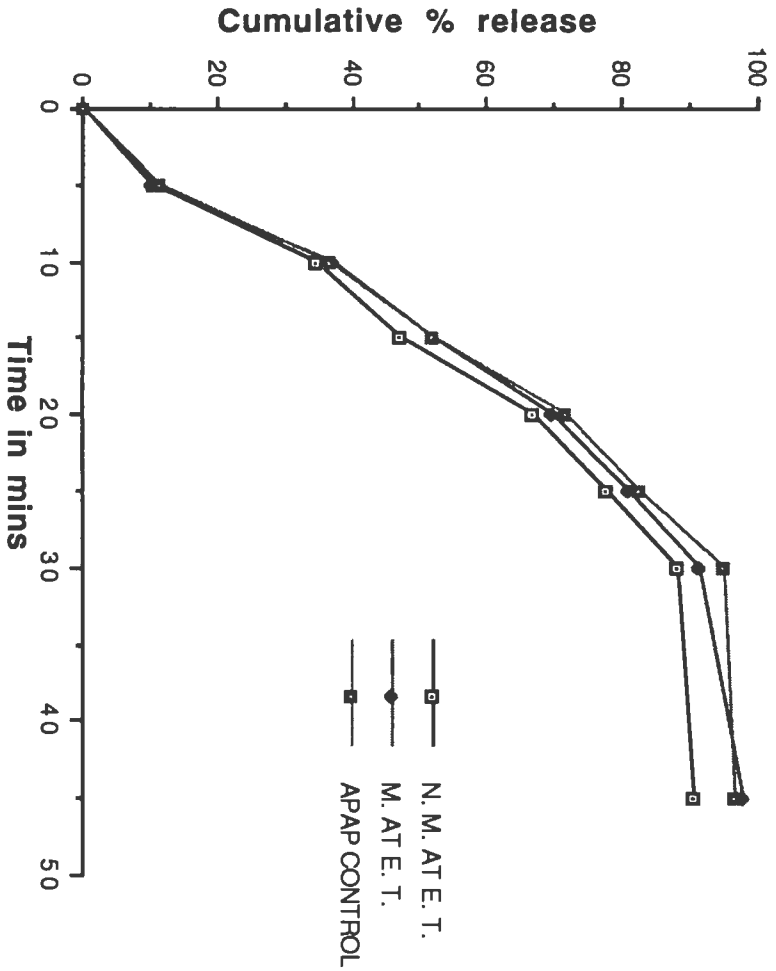

Cumulative % release
0
20
40
60
80
100
Time in mins
0
10
20
30
40
50
N. M. AT E. T.
M. AT E. T.
APAP CONTROL

FIGURE 12 Comparision of the dissolution profiles of microencapsulated and non microencapsulated acetaminophen in the tablet form at room temperature in presence of magnesium trisilicate.The abscissa indicates time in minutes and the ordinate shows cumulative percent release of the drug.The acetaminophen control is labelled as APAP CONTROL where as the dissolution profiles of non microencapsulated and microencapsulated acetaminophen are labelled as N. M. AT R. T. and M. AT R. T. respectively.

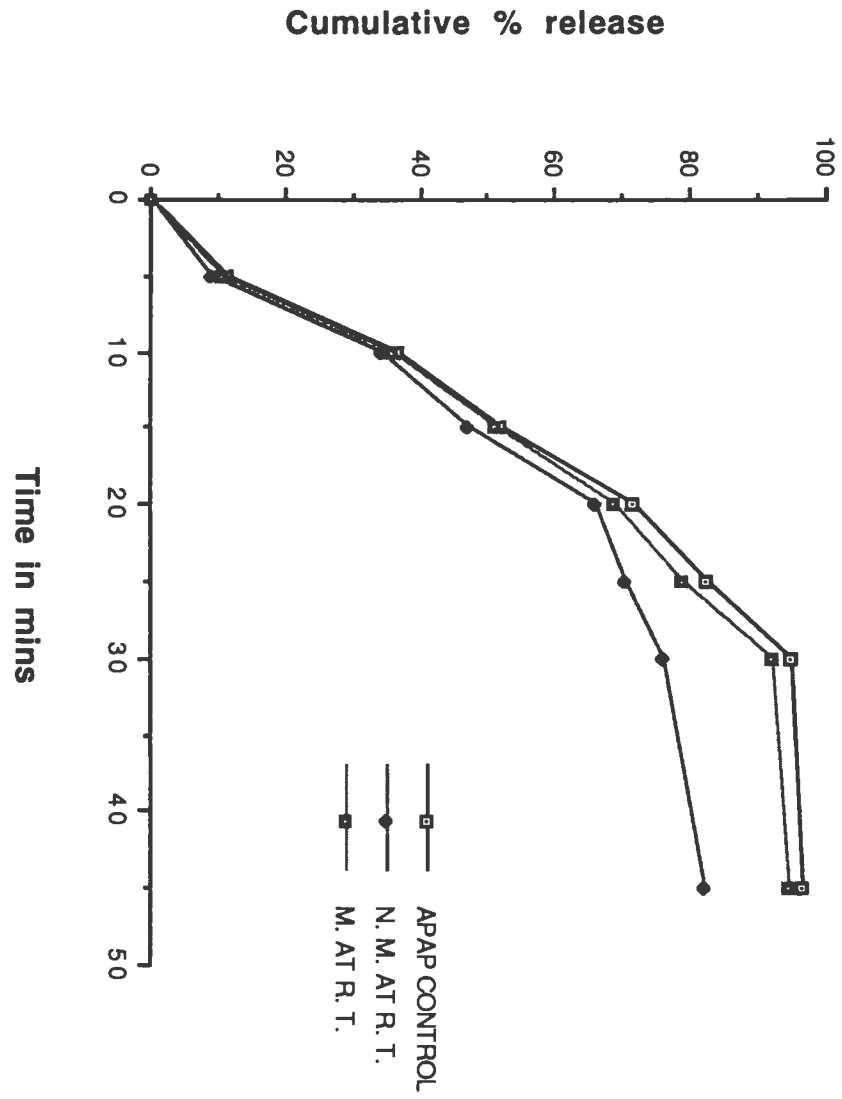
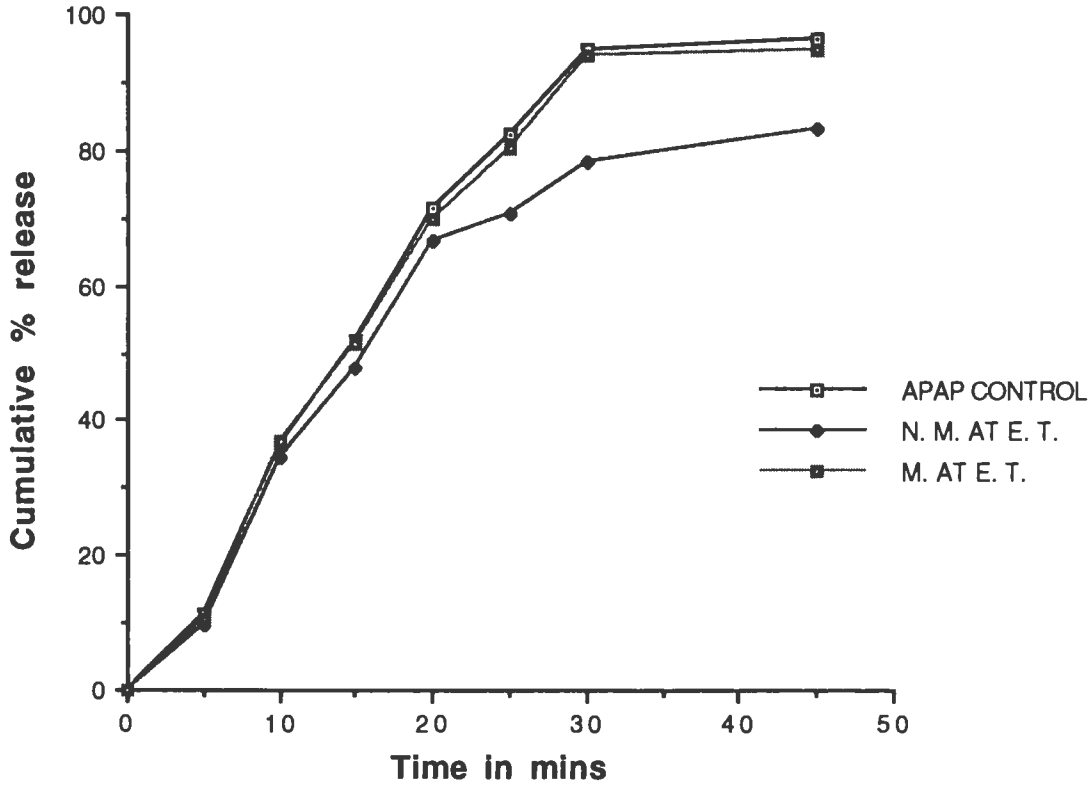

Cumulative % release
0
20
40
60
80
100
0
10
20
30
40
50
Time in mins
APAP CONTROL
N. M. AT R. T.
M. AT R. T.

FIGURE 13 Comparision of the dissolution profiles of microencapsulated and non microencapsulated acetaminophen in the tablet form at elevated temperature in presence of magnesium trisilicate. The abscissa indicates time in minutes and the ordinate shows cumulative percent release of the drug.The acetaminophen control is labelled as APAP CONTROL where as the dissolution profiles of non microencapsulated and microencapsulated acetaminophen are labelled as N. M. AT E. T. and M. AT E. T. respectively.


Cumulative % release
100
80
60
40
20
0
0
10
20
30
40
50
Time in mins
APAP CONTROL
N. M. AT E. T.
M. AT E. T.

DISCUSSION

In all the interaction studies carried out, it was demonstrated successfully that the microencapsulated drugs showed substantial reduction of the adverse effects of incompatibilities. The rate of degradation was significantly different for the microencapsulated and non microencapsulated systems. Though literature sources support the concept of enhancement of drug stability due to microencapsulation, there is absence of reliable published quantitative data which proves this point. Lot of material addresses this issue qualitatively. This study was focused on the quantitative aspects of the enhancement of stability due to microencapsulation.

All three drugs examined in this project showed significant stability when incorporated to microencapsules. However the level of protection was found to be different in all three cases. For acetaminophen the degree of protection was greatest followed by pseudoephedrine and aspirin. It was found that the level of protection offered by microencapsulated drugs in compressed tablets was greater than those found in the powder mixes. At the same time, the severity of the interaction was less in case of powders and was greater in case of compressed tablets. In case of tablets it was found that there was no effect of the compaction force on the integrity of the microcapsule coat. This observation could be supported by the fact that the tablets contained large amount of lactose which was used as a tablet matrix. This may have dispersed microencapsules and might have provided a cushioning effect which would protect the microencapsules from rupture during the compaction process. It would be interesting to see the effect of compaction force when the percentage of lactose to the microcapsules gradually decreases i. e. in a

tablet the amount of lactose goes on decreasing and the amount of drug remains same.

It was also observed that for the three compaction forces selected, the integrity of microcapsules was unaffected. This finding suggests that the Eurand microencapsules are sufficiently robust to be used commercially in compressed tablets without concern for capsule rupture. It may also be interesting to determine the effect of the increase in the percentage of microcapsules over the range of compaction forces.

It was found that the temperature affects significantly the results obtained between microencapsulated and non microencapsulated systems. The effect of time was not that pronounced. This observation was supported by the fact that the samples at elevated temperature were subjected to rigorous stress conditions (45 ^{0} C and 60 % relative humidity).

The decomposition of aspirin is due to hydrolysis which gave salicylic acid as a major hydrolytic product. The interaction takes place at room temperature and the rate of the reaction was enhanced by the increase in the temperature or the presence of moisture. The interaction was monitored in both these conditions. The assay involved the determination of the amount of drug remaining over an interval of time in powder mixes and compressed tablets. The analysis was done by UV at λ max. for aspirin. The figures obtained from both the data sets were compared and it was concluded that the degree of protection offered by microencapsulation was more in compressed tablets than in powders.

The interaction of acetaminophen with various antacids was a physical phenomenon of adsorption of the drug over the antacid. As indicated earlier

the rate of interaction differed significantly in powder form and compressed tablets. It was also found that the degree of adsorption was less at elevated temperature and more at room temperature. This observation can be supported by the fact that adsorption is a physical phenomenon and is affected by kinetics. The increase in temperature may result in the increase in the kinetic energy of the molecules, thereby increasing internal energy facilitating desorption.

It was observed that there is practically no interaction between aspirin and pseudoephedrine combination as well as pseudoephedrine acetaminophen combination. The inertness of the combination was apparent by the UV absorbance readings as well as by physical observations. The stability of the combination was retained at accelerated conditions. As pseudoephedrine itself was found to be stable with aspirin and acetaminophen, the same conclusion holds good for microencapsulated pseudoephedrine as the coating is made up of inert material.

The interactions of aspirin and pseudoephedrine were analyzed using statview statistical package. The method of analysis was Student's two tailed t test. Using this test, the difference in the microencapsulated and non - microencapsulated systems was easily demonstrated. The α value for this statistic was 0.01. The probability term calculated by t test was found very near to 0 indicating there is a very low probability that the results are similar between non microencapsulated and microencapsulated systems.

CONCLUSIONS

The conclusions made from the drug interaction studies can be enumarated as follows.

1) Aspirin showed significant degradation due to hydrolysis with Emcompress in powder mixes and direct compression tablets. The severity of this interaction was substantially reduced for aspirin in microencapsules

2) Aspirin does not show any compatibility problems when combined with acetaminophen. The combination is stable and does not show degradation in powder mixes as well as compressed tablets.

4) Aspirin does not interact with pseudoephedrine. Although the literature mentions the possibility of epimerization it was not observed in the laboratory experiments. The samples of aspirin - pseudoephedrine mixture were stable at room temperature as well as elevated temperature.

5) Acetaminophen reacts with antacids resulting in the adsorption of the drug over the antacid. The antacids tested were aluminum hydroxide, calcium carbonate and magnesium trisilicate. The severity of the interaction was found to be maximal in case of magnesium trisilicate and least in calcium carbonate. The response was similar in both powder mixes and compressed tablets. This interaction was eliminated completely when the drug was formulated in APAP Eurand microencapsules

6) There exist a characteristic interaction between acetaminophen and phenylephrine HCL & diphenhydramine HCL. Acetaminophen formed a eutectic mixture with these drugs resulting in melting point depression.

Microencapsules of acetaminophen gave physical protection against eutectic formation for both the drugs tested.

7) Pseudoephedrine does not show any interaction with acetaminophen and the mixture of these were found stable at room temperature as well as accelerated conditions. Microencapsulated acetaminophen gave similar results.

8) The statistical evaluation shows that there is a significant difference between the data sets obtained by the microencapsulated and non microencapsulated systems.

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APPENDIX A

Appendix A contains various calibration curves of microencapsulated and non - microencapsulated drugs.(Fig 1 to Fig 6). The method used for plotting the calibration curves involved UV spectrophotometric determinations at various concentrations. The absorbance values were determined at various concentrations and plotted as ordinates.

FIGURE 1 : Calibration curve of non - microencapsulated aspirin

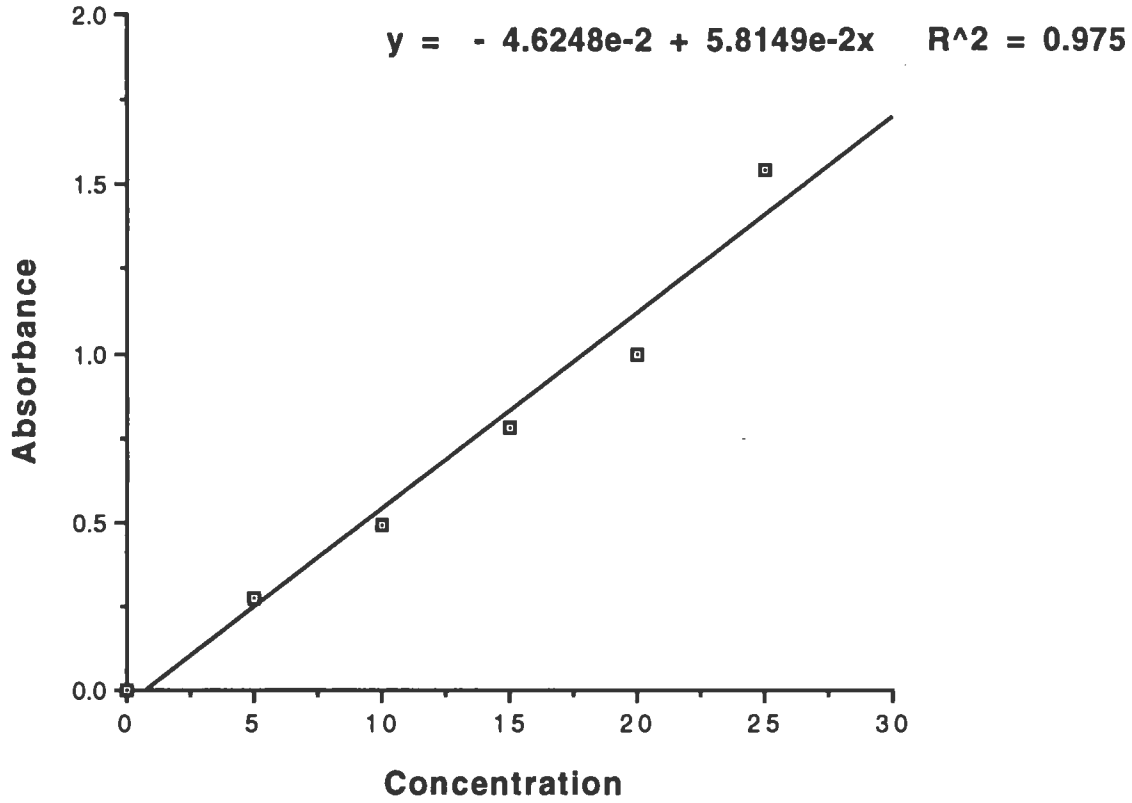


FIGURE 2 : Calibration curve of microencapsulated aspirin.

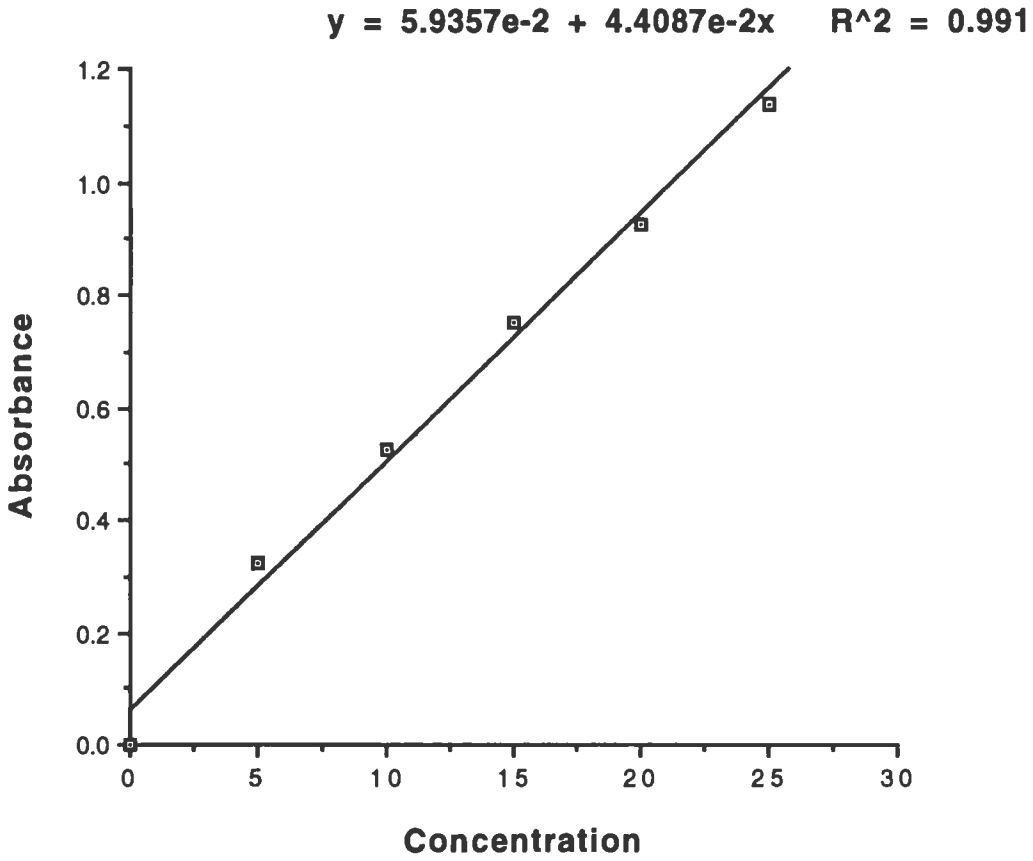


Figure 3 : Calibration curve of non microencapsulated acetaminophen.

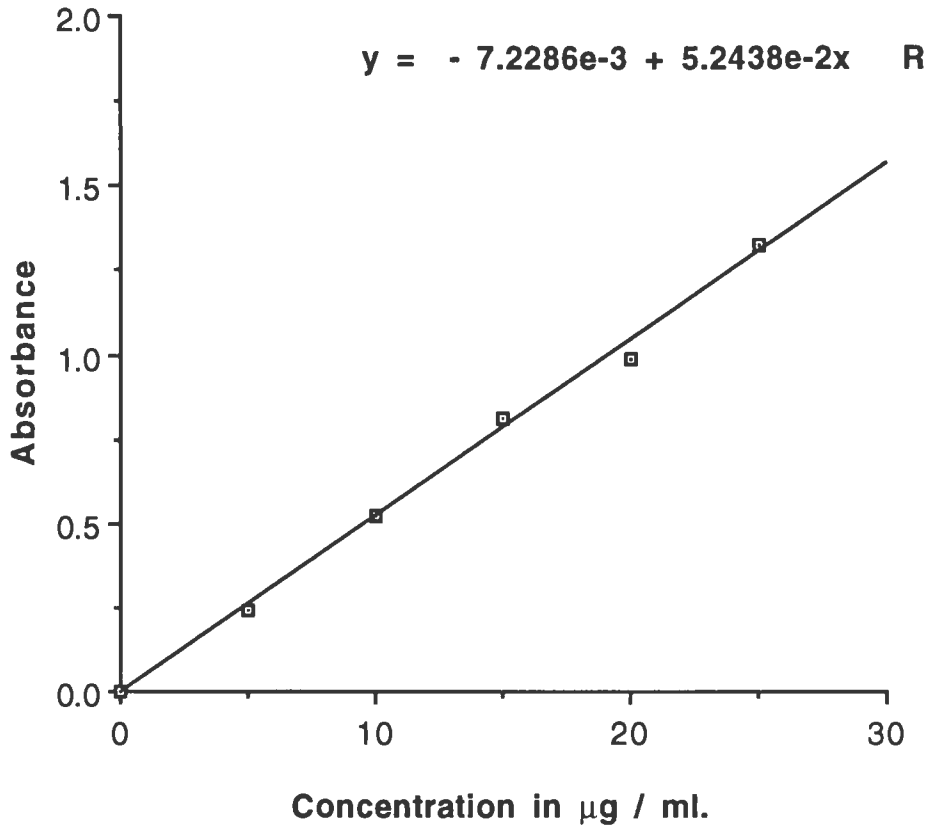


Figure 4 : Calibration curve of microencapsulated acetaminophen

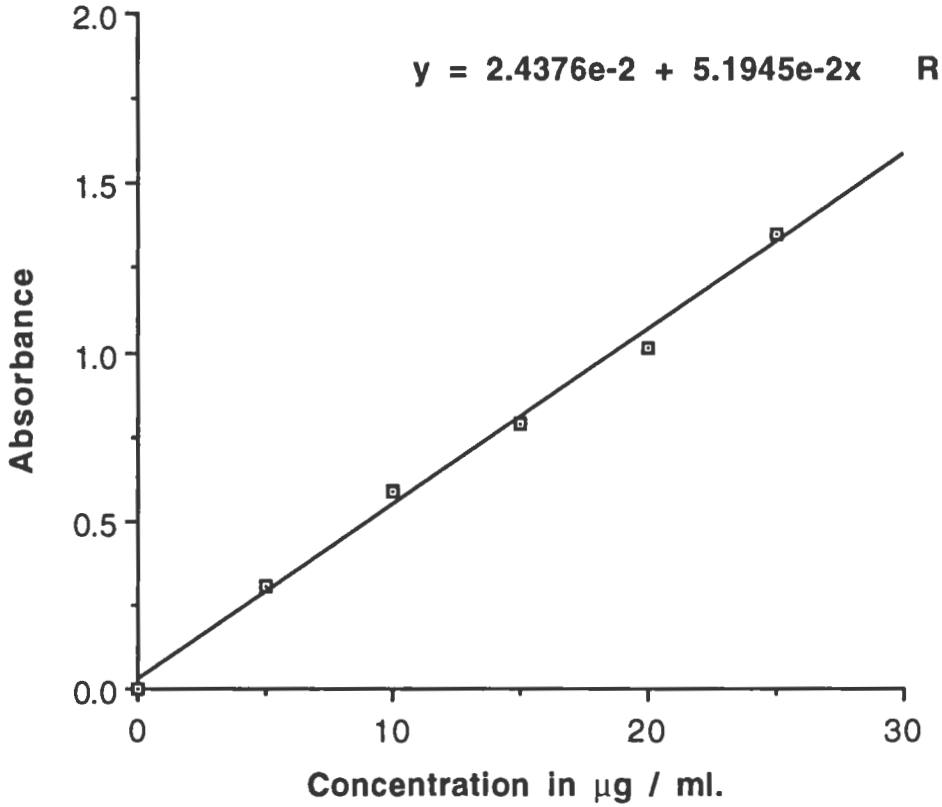


Figure 5 : Calibration curve of non microencapsulated pseudoephedrine hydrochloride.

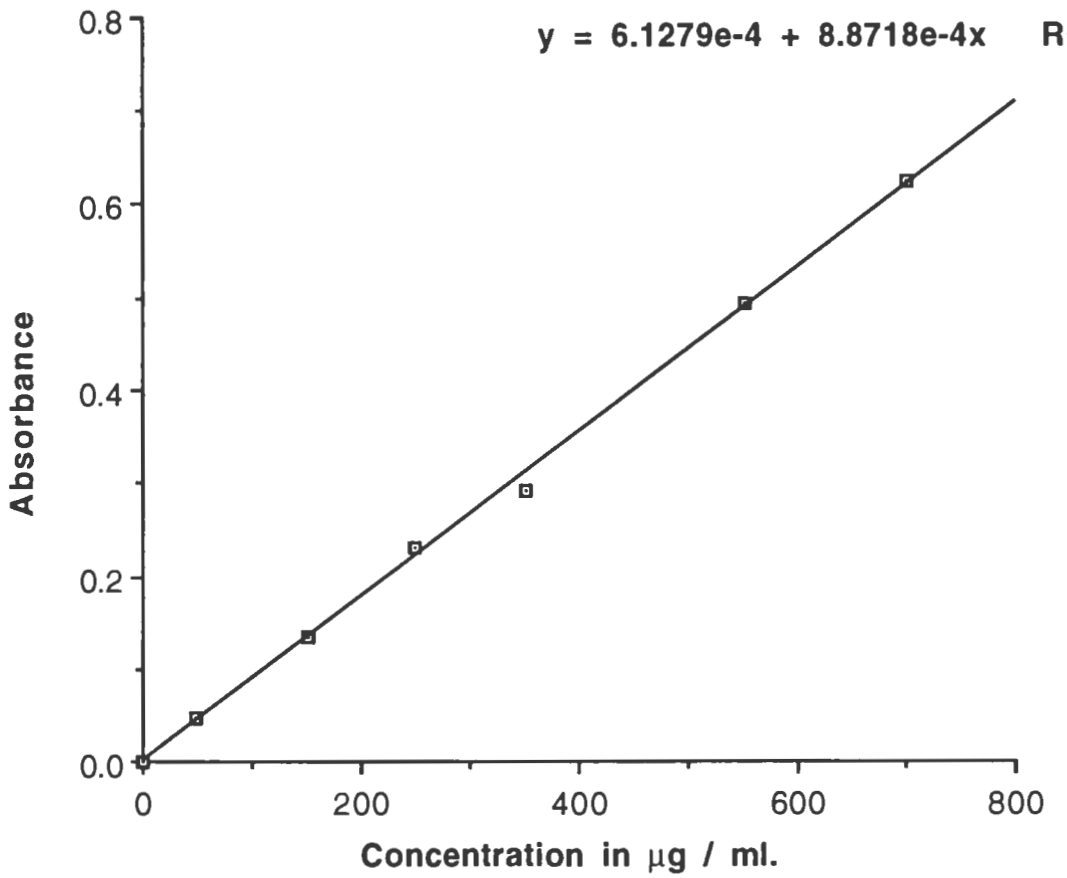
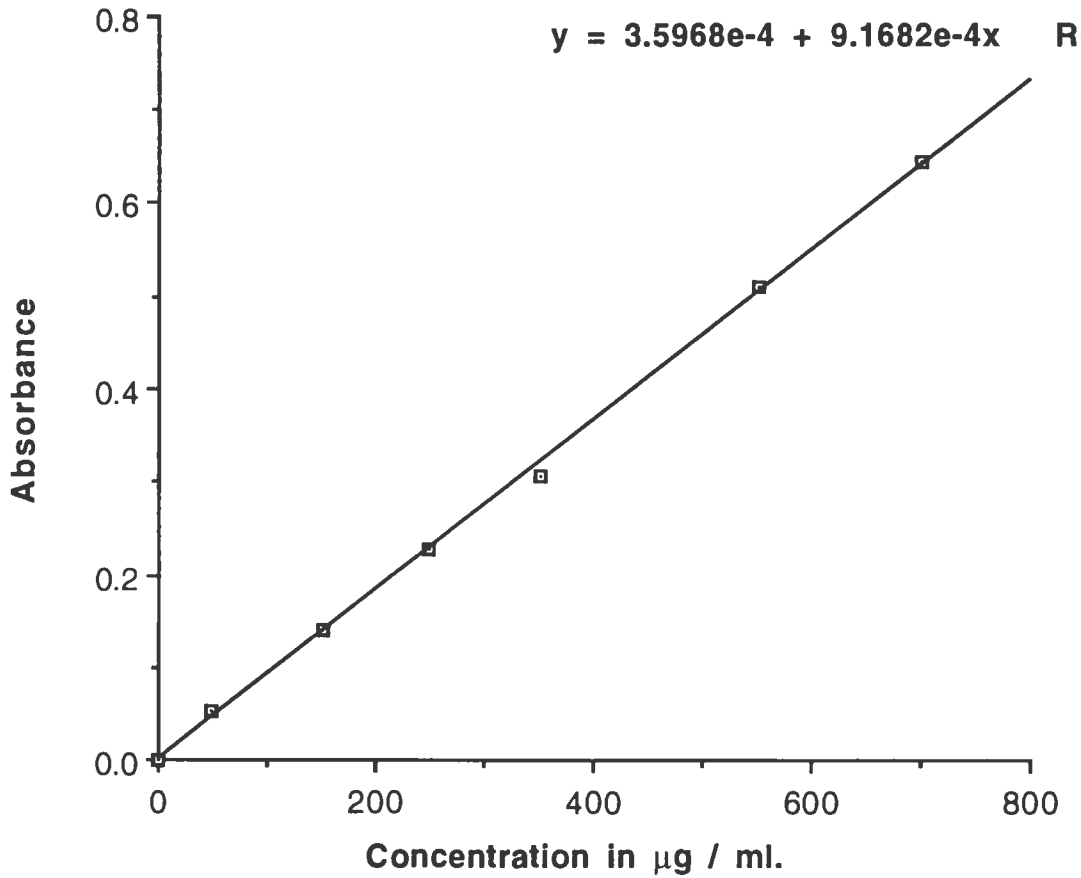


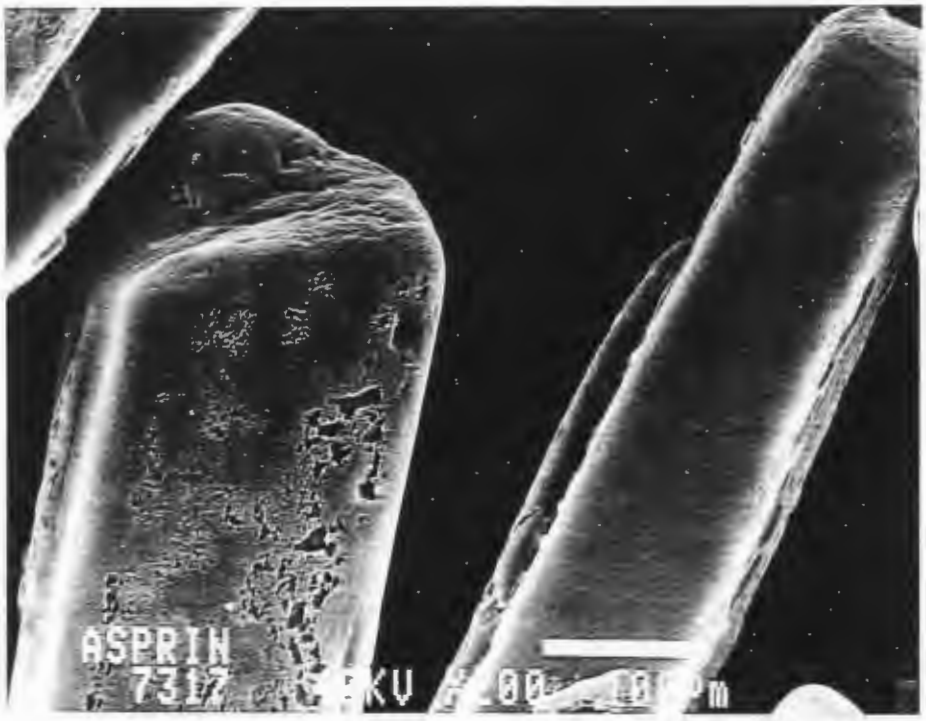
Figure 6 : Calibration curve of microencapsulated pseudoephedrine hydrochloride



APPENDIX B

Appendix B (Fig 7 to Fig 9) contains Scanning electron micrographs of aspirin, acetaminophen and pseudoephedrine hydrochloride at higher magnifications (200 and 3000) times. The procedure for obtaining these SEM is same as the one discussed under materials and methods.

FIGURE 7 : Scanning electron micrographs (magnified 200 and 3000 times) of aspirin microencapsules



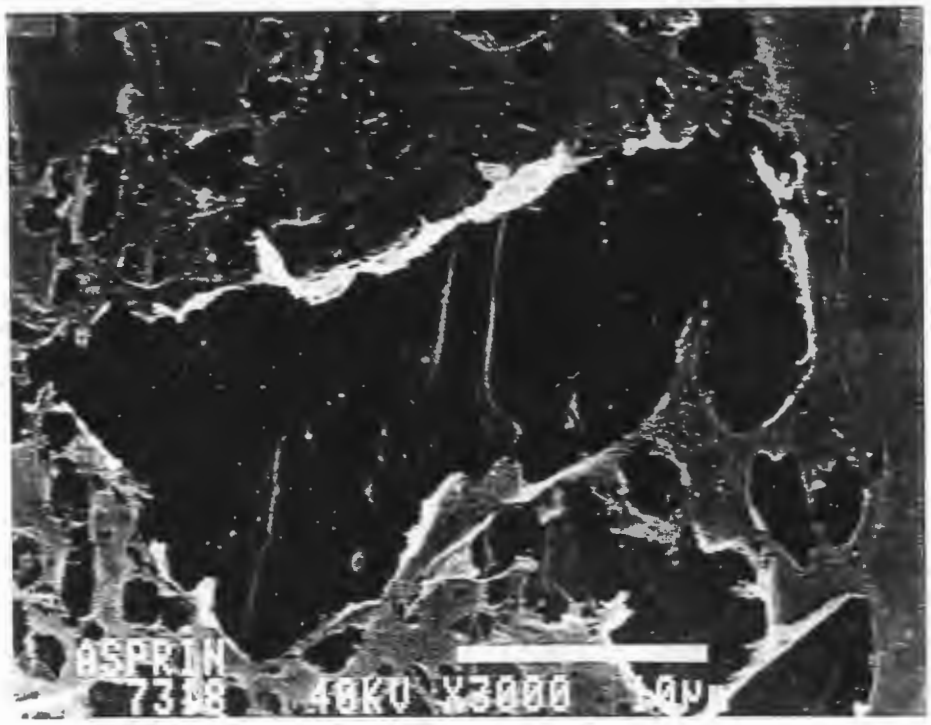
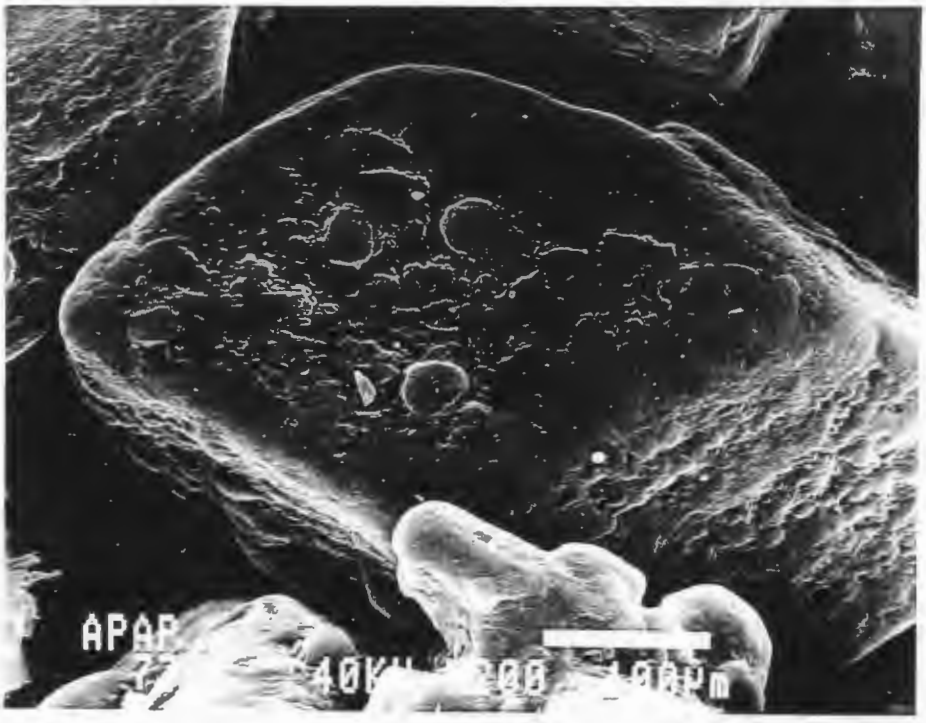


FIGURE : 8 Scanning electron micrographs of acetaminophen (magnified 200 and 3000 times) microencapsules.



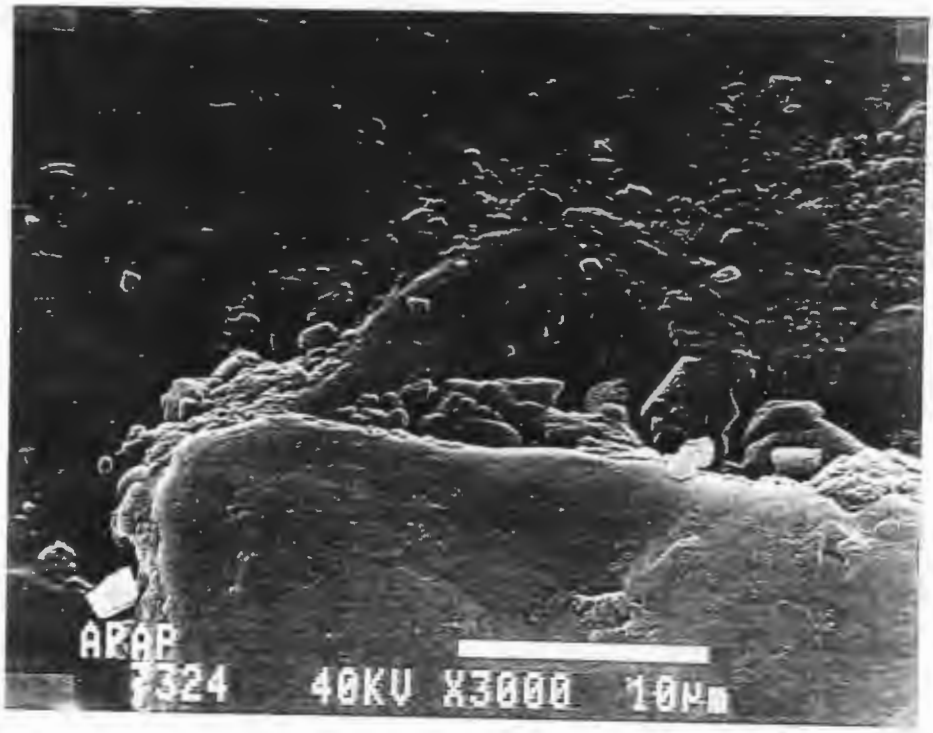
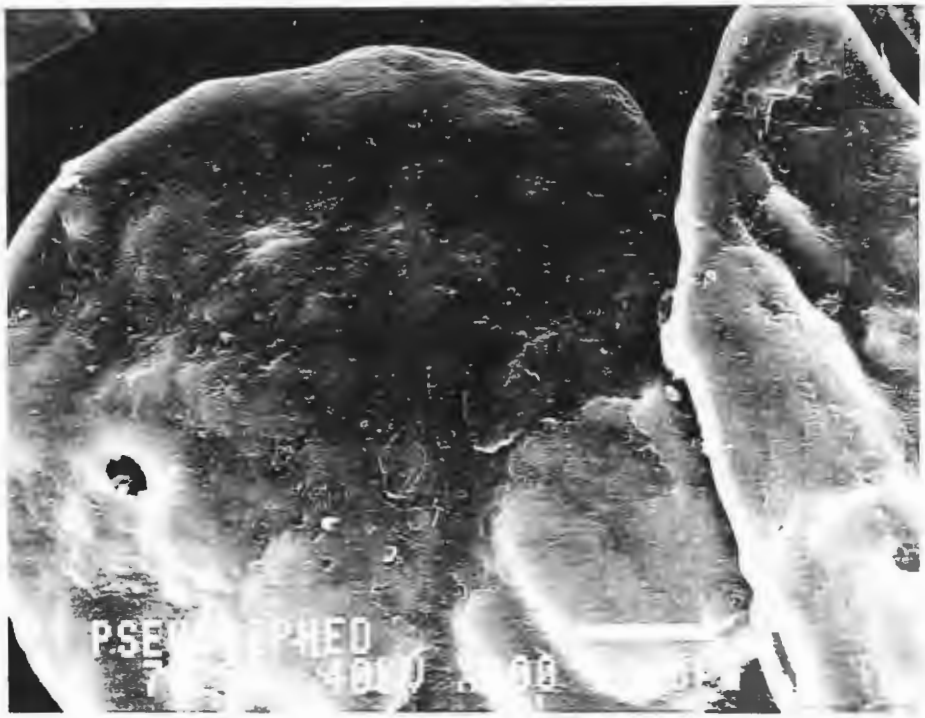
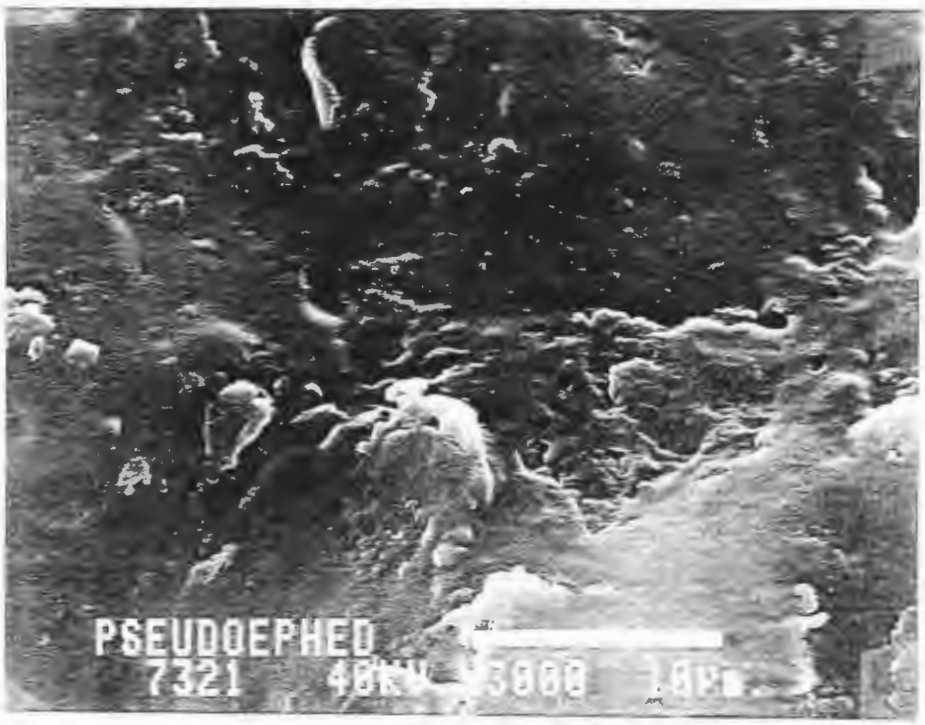


FIGURE 9 : Scanning electron micrographs of pseudoephedrine hydro chloride (magnified 200 and 3000 times) microencapsules





APPENDIX C

Appendix C contains

1) Dissolution data of acetaminophen with various antacids (Tables 1 to 3) in tablets.

2) UV analysis for the validation of the interaction between aspirin and Emcompress, for the determination of salicylic acid content. (Tables 4 to 8)

3) Calibration curve data for the figures in appendix A.(Tables 9 to 14).

TABLE 1 : Dissoultion data of acetaminophen and aluminum hydroxide tablets

Time in mins.	unencapsulated acetaminophen	unencapsulated acetaminophen	Encapsulated acetaminophen	Encapsulated acetaminophen
	Samples at room temp.	Samples at elevated temp.	Samples at room temp.	samples at elevated temp.
5	9.30 %	9.83 %	10.53 %	10.36 %
10	33.87 %	36.42 %	34.30 %	35.37 %
15	45.86 %	47.96 %	48.22 %	49.96 %
20	66.28 %	68.68 %	67.80 %	68.31 %
25	68.37 %	70.57 %	75.90 %	78.15 %
30	73.42 %	80.25 %	88.14 %	90.60 %
45	78.01 %	81.63 %	93.68 %	95.32 %

TABLE 2 : Dissoultion data of acetaminophen and calcium carbonate tablets:

Time in mins.	Unencapsulated acetaminophen	Unencapsulated acetaminophen	Encapsulated acetaminophen	Encapsulated acetaminophen
	samples at room temp.	Samples at elevated temp.	Samples at room temp.	Samples at elevated temp.
5	9.47 %	10.36 %	10.30 %	9.84 %
10	33.47 %	34.54 %	37.49 %	36.84 %
15	45.69 %	46.87 %	51.55 %	51.76 %
20	62.67 %	66.67 %	70.41 %	69.64 %
25	69.13 %	77.69 %	79.95 %	80.63 %
30	84.68 %	87.91 %	92.53 %	91.05 %
45	89.26 %	90.26 %	94.25 %	96.73 %

TABLE 3 : Dissolution data of acetaminophen and magnesium trisilicate tablets :

Time in mins.	Unencapsulated acetaminophen	Unencapsulated acetaminophen	Encapsulated acetaminophen	Encapsulated acetaminophen
	Samples at room temp.	samples at elevated temp.	Samples at room temp.	Samples at elevated temp.
5	8.91 %	9.66 %	10.44 %	10.63 %
10	34.13 %	34.18 %	35.92 %	37.07 %
15	47.00 %	47.86 %	50.94 %	51.54 %
20	65.97 %	66.71 %	68.60 %	69.92 %
25	70.29 %	70.78 %	78.71 %	80.18 %
30	75.83 %	78.47 %	91.97 %	94.02 %
45	81.84 %	83.28 %	94.21 %	94.95 %

Calculations for the determination of salicylic acid formed in the samples of aspirin by the method of simultaneous equations

Week 1

$A_{258} = 0.1631 = {}^{258}a_{aspirin} * b * c_{aspirin} + {}^{258}a_{sal.\ acid} * b * c_{sal.\ acid}$

$A_{302} = 0.002334 = {}^{302}a_{aspirin} * b * c_{aspirin} + {}^{302}a_{sal\ acid} * b * c_{sal.\ acid}$

putting the values for absorptivities as per Table 4 we get two simultaneous equations in two unknowns

$0.1631 = 0.00695\ C_a + 0.00157\ C_s$ ---------- (1)

$0.002334 = 0.00035\ C_a + 0.0276\ C_s$ ---------- (2)

Multiplying equation 2 by 19.85 we get

$0.0463 = 0.00695\ C_a + 0.05488\ C_s$ ---------- (3)

Subtracting (1) from (3) we get

$0.11685 = 0.5470\ C_s$

Therefore

$C_s = 0.2135\ \mu g / ml.$

Putting this value in equation (3) we get

$0.0463 = 0.00695\ C_a + 0.5488\ (0.2135)$

Therefore

C a = 0.1628 / 0.00695 = 23.426 µg / ml.

Thus concentration of aspirin remaining after one week in the sample is 23.426 µg / ml. and that of salicylic acid is 0.2135 µg / ml. These were the concentrations when the initial sample concentration was 25 µg / ml.

Similar calculations were done for samples stored upto 6 weeks at 45^0 C and the content of salicylic acid was determined. Similar calculations were done for the samples containing aspirin microencapsules. The results obtained are summarized in the Table 7 for the samples containing non - microencapsulated and in the Table 8 for the samples containing aspirin microencapsules.

TABLE 4 : Molar absorptivities of aspirin and salicylic acid

Compound	302 nm.	258 nm.
Aspirin	0.02765	0.00157
Salicylic acid	0.00035	0.000695

TABLE 5 UV analysis of samples containing non - microencapsulated aspirin as an avarage of three measurements. (Powder mix).

Time interval	258 nm	302 nm.
Week 1	0.1631	0.002334
Week 2	0.1536	0.0497
Week 3	0.1523	0.0509
Week 4	0.1509	0.0516
Week 5	0.1489	0.0529
Week 6	0.1477	0.0531

TABLE 6 UV analysis of samples containing microencapsulated aspirin as an avarage of three measurements (powder mix).

Time interval	258 nm.	302 nm.
Week 1	0.1721	0.004218
Week 2	0.1695	0.0501
Week 3	0.1618	0.0529
Week 4	0.1602	0.0566
Week 5	0.1587	0.0581
Week 6	0.1576	0.0598

TABLE 7 : UV analysis of samples containing non - microencapsulated aspirin as an average of three measurements :

Time interval	Aspirin (µg / ml.)	Salicylic acid (µg / ml.)
Week 1	23.426	0.2135
Week 2	21. 759	1.5222
Week 3	21.55	1.567
Week 4	21.35	1.5988
Week 5	20.98	1.6476
Week 6	20.877	1.656

TABLE 8 : UV analysis of samples containing microencapsulated aspirin as an average of three measurements :

Time interval	Aspirin (µg / ml.)	Salicylic acid (µg / ml.)
Week 1	24.22	0.1610
Week 2	24.047	1.510
Week 3	22.913	1.623
Week 4	22.652	1.760
Week 5	22.42	1.827
Week 6	22.25	1.881

TABLE 9 : Calibration curve data of non - microencapsulated aspirin

Concentration in μ G / ml.	Absorbance
0	0.000
5	0.2713
10	0.4917
15	0.7810
20	0.9989
25	1.5408

TABLE 10 : Calibration curve data of microencapsulated aspirin

Concentration in μ G. / ml.	Absorbance
0	0.00
5	0.3241
10	0.5243
15	0.7514
20	0.9270
25	1.1359

TABLE 11 : Calibration curve data of non - microencapsulated acetaminophen.

Concentration in μ G. / ml.	Absorbance
0	0
5	0.2376
10	0.5221
15	0.8136
20	0.9915
25	1.3247

TABLE 12 : Calibration curve data of microencapsulated acetaminophen.

Concentration in μ G. / ml.	Absorbance
0	0.00
5	0.3052
10	0.5825
15	0.7901
20	1.0116
25	1.3527

TABLE 13 : Calibration curve data of non - microencapsulated pseudoephedrine hydrochloride :

Concentration in μ G. / ml.	Absorbance
0	0
50	0.048
150	0.135
250	0.230
350	0.293
550	0.493
750	0.624

TABLE 14 : Calibration curve data of microencapsulated pseudoephedrine hydrochloride

Concentration in mcg. / ml.	Absorbance
0	0.00
50	0.052
150	0.141
250	0.228
350	0.306
550	0.510
700	0.645

APPENDIX D

Appendix D contains UV absorbance studies on the interaction between acetaminophen and pseudoephedrine hydrochloride.(Tables 15 to 18).

2) Interaction of pseudoephedrine with acetaminophen :

The combination of pseudoephedrine and acetaminophen was found to be stable at room temperature as well as accelerated conditions. The monitoring was done by UV spectrophotometric analysis.

Procedure :

a) For powder mixes kept at room temperature and accelerated conditions :

1) Weighed 200 gm. of pseudoephedrine and mixed with 200 gm. of acetaminophen in a turbula mixture at 90 RPM. for 30 mins.

2) Portions of 200 mg. were taken in 10 ml. open vial. The content uniformity of the samples were checked. It was in accordance with USP standards.

3) The samples were withdrawn initially and then at the regular intervals and the contents were analyzed spectrophotometrically in 0.1 N HCL.

4) The procedure was repeated for microencapsulated pseudoephedrine.

b) Compressed tablets at room temperature and accelerated conditions :

1) Granules were prepared by wet granulation method and were compressed on the carver press.

2) The tablets characteristics were checked for weight variation, content uniformity, hardness, thickness and friability.

3) The tablets were subjected to dissolution test in Vanderkamp 600

dissolution testing apparatus in 900 ml. of 0.1 N HCL at 100 RPM

4) The samples were removed after 5, 10, 15, 20, 25, 30, 45, 60, and 90 mins. and analyzed spectrophotometrically at 256 nm.

5) The rate of the interaction was determined in terms of the amount of pseudoephedrine remaining with respect to time.

TABLE 15 : UV absorbance data of pseudoephedrine hydrochloride and acetaminophen mixture in powder mixes at 45 C and 60 % R. H.

Conc.	week 1	week 2	week 3	week 4	week 5	week 6
50 µg/ml	0.0467	0.0451	0.0450	0.0457	0.0455	0.0451
150µg/ml	0.1329	0.1322	0.1311	0.1316	0.1310	0.1303
250µg/ml	0.2421	0.2419	0.2409	0.2411	0.2409	0.2401
350µg/ml	0.2969	0.2886	0.2881	0.2879	0.2876	0.2871
550µg/ml	0.5022	0.4997	0.4989	0.4981	0.4985	0.4981
700µg/ml	0.7021	0.7011	0.6994	0.6990	0.6993	0.6995

TABLE 16 : UV absorbance data of pseudoephedrine hydrochloride and acetaminophen mixture in powder mixes at room temperature :

Conc	week 1	week 2	week 3	week 4	week 5	week 6
50 µg/ml.	0.048	0.048	0.047	0.046	0.041	0.041
150µg/ml	0.135	0.133	0.133	0.131	0.131	0.130
250µg/ml	0.230	0.230	0.230	0.226	0.226	0.225
350µg/ml	0.293	0.291	0.291	0.288	0.289	0.289
550µg/ml	0.493	0.488	0.488	0.486	0.485	0.484
700µg/ml	0.634	0.622	0.622	0.619	0.617	0.609

TABLE 17 : UV absorbance data of pseudoephedrine hydrochloride and acetaminophen mixture in compressed tablets at 45 C and 60 % R. H.

Conc.	week 1	week 2	week 3	week 4	week 5	week 6
50 µg/ml.	0.0358	0.0347	0.0342	0.0336	0.0328	0.0319
150µg/ml	0.1227	0.1229	0.1220	0.1205	0.1211	0.1198
250µg/ml	0.2856	0.2855	0.2844	0.2736	0.2715	0.2629
350µg/ml	0.3319	0.3306	0.3258	0.3244	0.3221	0.3209
550µg/ml	0.5927	0.5919	0.5857	0.5749	0.5699	0.5633
700µg/ml	0.8088	0.8071	0.8027	0.8005	0.7986	0.7926

TABLE 18 UV absorbance data of pseudoephedrine hydrochloride and acetaminophen mixture in compressed tablets at room temperature :

Conc.	week 1	week 2	week 3	week 4	week 5	week 6
50 µg/ml.	0.0363	0.0352	0.0345	0.0341	0.0339	0.0328
150µg/ml	0.1215	0.1207	0.1191	0.1136	0.1028	0.1019
250µg/ml	0.2581	0.2491	0.2386	0.2297	0.2163	0.2159
350µg/ml	0.3266	0.3197	0.3171	0.3126	0.3121	0.3122
550µg/ml	0.5712	0.5692	0.5496	0.5478	0.5466	0.5468
700µg/ml	0.7889	0.7811	0.7791	0.7721	0.7714	0.7708

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